

An international consensus on an approach to the diagnosis and management of psychosis of suspected autoimmune origin: the concept of autoimmune psychosis

Thomas A. Pollak¹, Belinda Lennox², Sabine Müller³, Michael E. Benros⁴, Harald Prüss⁵, Ludger Tebartz van Elst⁶, Hans Klein⁷, Johann Steiner⁸, Thomas Frodl⁸, Bernhard Bogerts⁸, Li Tian^{9,10}, Laurent Groc¹¹, Alkomiet Hasan¹², Bernhard T. Baune^{13,14,15}, Dominique Endres⁶, Ebrahim Haroon¹⁶, Robert Yolken¹⁷, Francesco Benedetti¹⁸, Angelos Halaris¹⁹, Jeff Meyer²⁰, Hans Stassen²¹, Marion Leboyer²², Dietmar Fuchs²³, Markus Otto²⁴, David A Brown^{25,26}, Angela Vincent^{27*}, Souhel Najjar^{28*}, Karl Bechter^{29*}

¹Department of Psychosis Studies, Institute of Psychiatry, Psychology and Neuroscience, King's College London, UK

²Department of Psychiatry, University of Oxford, Warneford Hospital, UK.

³Department of Psychiatry and Psychotherapy CCM, Charité-Universitätsmedizin Berlin, Berlin, Germany

⁴Mental Health Center Copenhagen, Copenhagen University Hospital, Copenhagen, Denmark.

⁵Department of Neurology, Charité – Universitätsmedizin Berlin, and German Center for Neurodegenerative Diseases (DZNE) Berlin, CharitéCrossOver (CCO), Room 4-334, Charitéplatz 1, 10117 Berlin, Germany

⁶Department of Psychiatry and Psychotherapy; Medical Center - University of Freiburg, Faculty of Medicine; University of Freiburg, Germany

⁷University Groningen, Rob Giel Research Centre, Lentis and Northern Netherlands Addiction Research Affiliation: Euroweg 5, 9351 EM Leek, The Netherlands.

⁸Department of Psychiatry and Psychotherapy, Otto von Guericke University of Magdeburg, Leipziger Str. 44, 39120 Magdeburg, Germany & Center for Behavioral Brain Sciences (CBBS), Magdeburg, Germany

⁹Psychiatry Research Centre, Beijing Huilongguan Hospital, Peking University, Beijing, China

¹⁰Institute of Biomedicine and Translational Medicine, Department of Physiology, Faculty of Medicine, University of Tartu, Tartu, Estonia

¹¹Interdisciplinary Institute for NeuroSciences, CNRS UMR 5297, Université de Bordeaux 33077 Bordeaux, France

¹²Department of Psychiatry and Psychotherapy, University Hospital, LMU Munich, Germany

¹³Department of Psychiatry, Melbourne Medical School, The University of Melbourne, Melbourne, Australia;

¹⁴The Florey Institute of Mental Health and Neurosciences, The University of Melbourne, Parkville, Australia;

¹⁵Department of Psychiatry, University of Münster, Münster, Germany;

¹⁶Department of Psychiatry and Behavioral Sciences, Emory University School of Medicine, 101 Woodruff Circle Suite 6003, Atlanta, GA 30322, USA.

¹⁷Stanley Neurovirology Division. Department of Pediatrics, Johns Hopkins School of Medicine, Baltimore Md USA.

¹⁸Psychiatry and Clinical Psychobiology, Division of Neuroscience, Scientific Institute Ospedale San Raffaele, Milano, Italy; University Vita-Salute San Raffaele, Milano.

¹⁹Department of Psychiatry, Loyola University Medical Center, Maywood, Illinois, USA

²⁰Research Imaging Centre, Campbell Family Mental Health Research Institute, Centre for Addiction and Mental Health, and Departments of Psychiatry; Pharmacology and Toxicology; and Institute of Medical Science; Toronto, Ontario, Canada.

²¹Institute for Response-Genetics, Psychiatric University Hospital (KPP), Zurich, Switzerland

²²Department of Psychiatry and Addiction, Mondor University Hospital, University Paris-Est-Créteil (UPEC), Inserm U955, Créteil, France.

²³Division of Biological Chemistry, Biocenter Innsbruck Medical University Innrain 80, 4th Floor, Room M04-313 A-6020 Innsbruck, Austria

²⁴Department of Neurology, University clinic, Oberer Eselsberg 45, 89081 Ulm, Germany

²⁵Department of Immunopathology, ICPMR, New South Wales Health Pathology, Department Clinical Immunology Westmead Hospital;

²⁶Centre for Immunology and Allergy Research, The Westmead Institute for Medical Research, University of Sydney, Westmead NSW Australia,

²⁷Nuffield Department of Clinical Neurosciences, John Radcliffe Hospital, Oxford OX3 9DU

²⁸Department of Neurology, Zucker School of Medicine at Hofstra/Northwell, Lenox Hill Hospital, New York, NY 10075

²⁹Dept. Psychiatry and Psychotherapy II, Ulm University, Bezirkskrankenhaus Günzburg, Germany

Corresponding author(s):

Dr T A Pollak, Department of Psychosis Studies, Institute of Psychiatry, Psychology and Neuroscience, King's Health Partners, King's College London, De Crespigny Park, Denmark Hill, London SE5 8AF, UK, Tel: +44 (0) 207 848 5135, Fax: +44 (0) 207 848 0572, Email: thomas.pollak@kcl.ac.uk

***Senior authors**

Abstract (150 words max)

There is increasing recognition in the neurological and psychiatric literature of patients with ‘isolated’ psychotic presentations (i.e. with no, or minimal, neurological features) who have tested positive for neuronal autoantibodies (principally NMDA receptor antibodies), some of whom have responded to immunotherapies. While these individuals are sometimes described as having an atypical, mild or attenuated form of autoimmune encephalitis, some authors feel that that these cases are sufficiently different from typical autoimmune encephalitis to establish a new category of ‘autoimmune psychosis’. We briefly review the background, discuss the existing evidence for a form of autoimmune psychosis, and propose a novel, conservative approach to the recognition of ‘possible’, ‘probable’ and ‘definite’ autoimmune psychosis for use in psychiatric practice. We outline the investigations required and the appropriate therapeutic approaches, both psychiatric and immunological, for probable and definite cases, and mention ethical issues posed by this challenging new diagnostic category.

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Introduction

Human and experimental data indicate diverse immunological and inflammatory abnormalities in subgroups of individuals diagnosed with a broad range of severe psychiatric disorders; these include new-onset psychosis and schizophrenia¹⁻⁵, defined according to the currently established DSM/ICD criteria. These aberrant inflammatory and immunological responses may not only contribute to the psychiatric and behavioral problems, but also to the accompanying cognitive impairment, soft neurological signs, and autonomic abnormalities^{3,6}. They could also contribute to disease severity as well as the substantial proportion of patients who demonstrate an inadequate response to the conventional antipsychotics or psychotherapies^{3,7}. Moreover, the recent discoveries of antibodies to neuronal surface proteins in autoimmune encephalitis (AE) have generated a great deal of interest in the possibility that some psychiatric patients, in particular those with both affective and nonaffective psychoses, have a specific autoantibody-mediated disease or 'autoimmune psychosis'⁸⁻¹⁰.

Parallel to previously published criteria and guidelines providing a clinical approach to the diagnosis of probable and definite AE¹¹, here we aim to develop an approach to the identification of psychosis of possible or probable autoimmune origin. The full aims of the current paper are summarized in Box A.

Methods

An initial working draft was developed by KB, and subsequently discussed at two round table sessions at the 14th Psychoimmunology Expert Meeting (<http://www.psychoimmunology-experts.de/>) at Günzburg, Germany, in March 2018. All co-authors contributed to the working draft, three circulations of the subsequent drafts, and agreed the final submission and revision (supplemental appendix A).

Evidence linking inflammation, immune dysregulation, and autoimmunity to psychosis neurobiology

There is growing evidence linking low-grade neuroinflammation and immune dysfunction to the pathophysiology of psychosis in a subset of individuals diagnosed

with acute psychosis or schizophrenia-spectrum disorders ^{7,12-15}. Table 1 summarizes findings that include clues from genetics, infections, inflammatory markers and neuropathology. The most relevant recent findings include identification of multiple immune-related loci of the MHC complex including the complement system (also implicated in synaptic pruning during neurodevelopment) ¹⁶⁻¹⁸, increased frequency of autoimmunity in the subject or family members ¹⁹⁻²² and the existence of serum and cerebrospinal fluid (CSF) biomarkers of inflammation ^{1,23}. The latter identify increased permeability of the blood-brain barrier (BBB) with neuroinflammation and neurovascular unit abnormalities that could initiate brain infiltration of immune mediators ^{24,25}.

Although highly suggestive, and supported by the limited post-mortem studies on brains from patients with schizophrenia which have documented upregulated inflammatory mediators and microglial activation ², there are infrequent studies looking for lymphocytic infiltration, IgG deposition and hippocampal involvement ^{4,5,26,27}. The possibility of an adaptive immune response to specific neuronal receptors has, however, become a major interest since the description of autoimmune forms of encephalitis.

Autoimmune encephalitis and findings in patients with psychosis

Typically, in addition to psychiatric disturbance patients with AE develop clear neurological features including seizures, cognitive dysfunction and movement disorders ²⁸. These patients have potentially pathogenic antibodies that target specific synaptic and related proteins, expressed on the cell surface, principally the N-methyl-D-aspartate receptor (NMDAR, specifically the NR1 subunit) and the voltage-gated potassium channel (VGKC)-complex proteins, leucine-rich-glioma inactivated 1 (LGI1) and contactin-associated protein-like 2 (CASPR2) ²⁸⁻³⁰. The clinical associations of these and other antibodies are described in Table 2. The neuronal autoantibodies can be measured routinely using cells that express the specific antigen and are fixed for distribution to the clinical laboratories who test the patient samples for presence of IgG binding to the cells. Research techniques and comments about other assays are described in Supplementary material.

These IgG neuronal surface antibodies bind to extracellular epitopes on the target membrane proteins and, when bound to live neurons or other antigen-expressing

cells, they lead to divalent cross-linking, resulting in internalisation and loss of surface expression ^{31,32}, or less frequently direct inhibition of receptor function ³³. Most studies have not addressed complement-activation or possible cell-mediated immune mechanisms and the neuropathological studies in AE are limited.

In some individuals, behavioral and psychiatric disturbance dominate the course of AE ^{34,35} leading to studies looking for these antibodies in patients with primary psychiatric disorders such as schizophrenia and first-episode psychosis (FEP).

Neuronal autoantibody studies in psychotic disorders

Most studies have concentrated on NMDAR-Abs because the associated encephalitis has the strongest association with psychiatric features, an incidence that mirrors the age-related incidence of psychotic disorders, and a pathophysiology compatible with the glutamate hypothesis of schizophrenia ³⁶. The results in psychiatric patients have largely been restricted to sera. In one meta-analysis, the prevalence of IgG NMDAR-Ab seropositivity in serum among individuals with first-episode psychosis (FEP) varied from 0-12% and in some cases the frequencies and titres of positive antibodies were not different from controls ³⁷. However, studies varied in duration of psychiatric disease, age of the patients, and particularly the antibody tests used. These included detection of IgG, IgA and IgM antibodies binding to the commercial fixed cell assays (described above) and found mostly IgA or IgM, for which pathogenicity is unclear ³⁸. Others used research methods involving IgG binding to live cells expressing the NMDAR subunit(s), binding of IgG to the hippocampal region on rodent brain tissue sections, and/or binding of IgG to the surface of live rodent hippocampal neuronal cultures. These two latter approaches are useful for confirming the specificity and potential clinical relevance of serum IgG autoantibodies in AE ³⁹ when CSF studies are not available.

CSF studies are indeed very rare in patients with psychosis and the significance of serum antibodies detected with the fixed assays is not always clear. This is particularly the case given that multiple studies have demonstrated serum neuronal autoantibodies to be nonspecific to AE, detecting them in various patient groups and healthy individuals, when they are unlikely to be clinically relevant ⁴⁰. In the following sections we use the term 'seropositive psychosis' to refer to any case of psychosis that is seropositive for neuronal surface autoantibodies, but this alone should not

assume causation or exclude the possibility that there may be alternative mechanisms.

Clinical psychiatric presentation and history of patients with AE or possible AP

In NMDAR-Ab encephalitis, patients present with a polymorphic psychosis with prominent affective symptoms and cognitive impairment, but negative psychotic symptoms may also feature with depression and suicidality relatively common ⁴¹⁻⁴³. Importantly, the presentation of patients with NMDAR-Ab encephalitis, according to current diagnostic criteria ¹¹, rarely maps easily onto existing diagnostic constructs for schizophrenia-spectrum disorders ^{41,43-45}. Moreover, the majority of studies have failed to find clinically meaningful differences in severity across multiple symptom domains between seropositive and seronegative subjects with psychosis ⁴⁶⁻⁴⁸.

CSF examinations in AE and AP

In AE, CSF positivity, which demonstrates substantial intrathecal synthesis of NMDAR-Abs in most patients, is considered necessary and sufficient for a diagnosis; indeed pathogenic NR1-antibodies have been cloned from CSF B cells ⁴⁹. However, in psychosis, CSF studies are rare ^{50,51} and in most undifferentiated psychosis cohorts the proportion of seropositive cases who are also CSF positive is highly variable (0% to 75% ⁵²⁻⁵⁴). This may be partly due to lower antibody levels and use of different tests, increasing the difficulties in interpreting the clinical significance of the findings ⁵⁵, but may also reflect lack of intrathecal synthesis in some cases. An additional consideration, not widely considered, is that CSF antibodies may not be detectable due to their absorption by the relevant antigen in the brain⁵⁶.

More generally relevant is the existence of pleocytosis. CSF lymphocytes are, typically, moderately increased in NMDAR-Ab encephalitis and some other forms of AE, mainly during the early stages with oligoclonal bands appearing later ⁵⁷. Frank lymphocytosis (of >5 WBCs/mm³) is generally under 5% in undifferentiated psychosis cohorts ^{50,51}, without comparison to control groups. Only two recent studies have reported CSF abnormalities (including pleocytosis, raised protein or the presence of oligoclonal bands) in NMDAR-Ab seropositive psychosis individuals ^{52,54}; these findings need to be extended to paired serum and CSF samples in large cohorts of patients.

Neuroimaging findings

Limbic encephalitis is the classical form of AE and is associated with unilateral or bilateral hippocampal MRI FLAIR-T2 hyperintensities, with or without transient contrast enhancement, in the medial temporal lobes ^{11,58,59}. By contrast, MRI features are neither sensitive (only 40%), specific (mainly non-specific white matter changes) or necessary for the diagnosis of NMDAR-Ab encephalitis ⁶⁰, and structural abnormalities are rare ⁵⁹ (Figure 1). MRI findings in seropositive psychosis cases have not been helpful to date ^{52,53}. Cortical FDG hypometabolism (Figure 1) or hypermetabolism can both be found in AE and could be indicative of active and persistent neuroinflammatory processes ^{2,61} but FDG-PET studies have not been performed in seropositive psychosis.

Similarly pathological EEG findings such as diffuse slowing, intermittent rhythmic delta or theta activity, or clear epileptiform discharges are neither very sensitive nor specific for AE ⁶². These EEG features have been described in small but relevant subgroups of patients with schizophrenia, depression and schizoaffective disorders ⁶³. Interpretation of such abnormalities, however, is confounded by the effects of psychiatric (particularly antipsychotic) drugs on the EEG. By contrast, a very typical EEG pattern, extreme delta brush (delta waves with superimposed beta waves (brush), EDB) ⁶⁴ has been observed in 6.7% of NMDAR-Ab patients ⁶⁵; although only rarely seen in patients with isolated psychotic presentations and NMDAR-Abs in CSF or serum, occasionally in a less widespread ‘EDB-like pattern’ with fast waves superimposed on delta waves ^{53,66,67} (Figure 2), it is a potentially important sign of NMDAR-Ab pathology.

Potential association with infections and systemic autoimmunity

Infections have long been thought to be a risk factor for autoimmunity and prodromal infections are evident in AE and psychotic disorders ^{68,69}. Most striking is the history of a preceding herpes simplex viral encephalitis (HSVE) in NMDAR-Ab mediated encephalitis ⁷⁰⁻⁷². CNS infection might therefore be a possible initiator of AP ⁷³, a possibility that is consistent with a considerable body of evidence implicating infections in the aetiology of psychotic disorders (Table 1).

Although there are associations between psychosis and several classical autoimmune disorders (see above), including neuropsychiatric lupus, the frequency of ANA and thyroid antibodies in the general population precludes their relevance in defining possible AP. Equally, psychotic features are not infrequent in patients with classical paraneoplastic syndromes, but they are seldom isolated and the utility of antibody testing in individuals with isolated psychiatric presentations remains unclear^{74,75}.

Consensus multi-modal approach to the systematic investigation of patients with suspected autoimmune psychosis

Collectively, the observations summarised briefly above point to a potential overlap between AE-associated psychosis and psychotic disorders^{76,77}, prompting some authors to adopt the term mild encephalitis⁷⁸ or autoimmune psychosis (AP)¹⁰, as a possible incomplete or “*forme fruste*” of AE with dominant psychotic features². Acknowledging that debate exists regarding appropriate terminology⁷⁹, here we use AP and propose a clinical approach to the identification of patients with possible, probable or definite AP within psychiatric practice.

In Box B, we propose diagnostic criteria for AP. These criteria are necessarily conservative in terms of the support required from clinical and paraclinical investigations. They demarcate a group of patients about whom we agree have a possible, probable or definite autoimmune aetiology to their psychotic disorder. As such, there is overlap with existing consensus criteria for AE¹¹. These AP criteria are less stringent from a symptomatic viewpoint than the existing AE criteria, mainly in including patients with an isolated psychotic presentation, but they are consequently more stringent in terms of paraclinical evidence required for diagnosis, so that the possibility of misdiagnosis (and inappropriate treatment) is minimised.

The current criteria for ‘definite NMDAR-Ab encephalitis’ diagnose a patient with acute psychosis and serum NMDAR-Abs as having encephalitis, provided that these serum antibodies demonstrate binding to live neurons or brain slices. We have in our laboratory work identified healthy individuals with serum NMDAR-Abs that bound cultured hippocampal neurons (TP, AV, unpublished data), and so we suggest that *additional* paraclinical evidence is required in the case of a positive serum antibody without confirmatory CSF.

It is possible that the criteria which we outline in Box A may be *too* conservative, excluding potential AP patients who present with a) a more chronic psychotic picture (i.e. more than 3 months); b) none of the symptomatic criteria (i.e. no ‘red flags’) or c) normal EEG, MRI and CSF findings, but establishing that these patients exist and might respond to immunotherapies must await future developments. Nevertheless, if such cases raise clinical concern, they should be individually discussed with clinicians with appropriate expertise. For the present, we propose these criteria and consider their validation to be a research priority.

Note that the criteria do not exclude a diagnosis being made in a patient with an acute onset (<3 months) of psychosis even if that patient has had a previous psychotic, other psychiatric or encephalopathic episode that resolved. This is consistent with case reports of patients with previous (single or multiple) episodes of psychiatric symptoms the most recent of which was diagnosed as AE⁸⁰⁻⁸⁴, as well as evidence that relapses of NMDAR-Ab encephalitis (which can occur up to 13 years later⁸⁵) are more likely to present with isolated psychiatric symptoms³⁴.

Clinical history and mental state examination

A number of authors have proposed lists of clinical ‘red flags’ (and some have proposed ‘yellow flags’) that should raise suspicion of CNS autoimmunity (in particular NMDAR-Ab encephalitis) in patients presenting with psychosis^{9,62}. These ‘red flag’ elements, similar to those in AE, are summarized in Box C. Notably, they are not individually uncommon in psychotic disorders, although may be mild in severity (see table 2 in ⁹). There are however cases of CNS autoimmunity presenting with psychiatric symptoms and histories that are indistinguishable from so-called ‘nonorganic’ or functional psychoses, and a ‘red flag’ approach might miss cases of potentially immunotherapy-responsive AP. Rather than suggest that *all* cases of acute psychosis be screened for neuronal autoantibodies or other evidence of CNS autoimmunity⁸⁶, here we consider only testing for antibodies in the presence of *specific* red flags to be clinically *mandated*. We suggest that testing for CNS autoimmunity in all other cases happens *at the clinician’s discretion*.

Detection of IgG antibodies in serum and CSF

When a patient meets criteria for 'possible AP', antibody tests should be performed on both serum and CSF and include, if possible, all neuronal surface autoantibodies and paraneoplastic antibodies, if clinically indicated [see Table 2]. There are commercial multiplexed assays for multiple testing, which should include NMDAR, LGI1, CASPR2, GABA_AR, GABA_BR and AMPAR autoantibodies. Voltage-gated potassium channel antibodies by radioimmunoprecipitation should not be specifically requested as a positive result can be clinically irrelevant^{87,88}; LGI1 and CASPR2 are the functionally relevant antigens. If not available, choice of which autoantibody to test will also depend on the clinical presentation of the patient: eg. movement disorders (commonly NMDAR, rarely LGI1 and CASPR2), hyponatraemia (LGI1 and CASPR2), a diarrhoeal prodrome (DPPX). If only serum is available, the conclusions drawn should be more cautious and in these cases, or if the patient does not have an antibody detectable in CSF, *positive evidence from other steps are required to make a diagnosis of AP (see Box B).*

Confirmatory testing with additional immunoassays (to demonstrate binding to live neurons or reactivity with brain tissue^{11,61,89}) is desirable but not essential for a diagnosis of probable AP if there is other positive paraclinical/laboratory evidence such as encephalopathic EEG or CSF pleocytosis. However, positivity on the confirmatory immunoassays can be useful when other paraclinical findings are unavailable or show only borderline abnormalities.

CSF biomarkers of inflammation or immune activation

Pleocytosis (> five WBCs per mm³), presence of OCBs, and elevated IgG index should be sought. Where possible, careful IgG concentrations and antibody titres on parallel CSF and serum will allow calculation of intrathecal production of specific antibodies. However, intrathecal production and high CSF antibody levels, although common in some forms of AE (e.g. with NMDAR, GABA_BR and AMPAR antibodies), are less common in others (e.g. with LGI1 and CASPR2 antibodies).

Other serum or neuroimaging biomarkers of inflammation and autoimmunity

Anti-nuclear antibody (ANA) and anti-double-stranded DNA (dsDNA) are useful to screen for co-existing SLE and other systemic autoimmune disorders, particularly in those with clinical evidence of systemic autoimmunity. Whereas ANA is frequently

positive in healthy individuals dual positivity with dsDNA is far more specific. The pathogenicity of thyroid antibodies remains unknown although their association with steroid responsiveness is more established. Thus, thyroid antibodies seropositivity in isolation is not sufficient for AP diagnosis, but would provide further support for AP in those who satisfy probable AP criteria ⁹⁰.

MRI

This is essential both to look for signs of inflammatory changes and to exclude other etiologies, such as infections, tumours or other brain inflammatory disorders, particularly demyelinating diseases and vasculitis. The recommended MRI protocol overlaps with that used for infectious causes of encephalitis ⁹¹. Crucially, negative MRI does not preclude an autoantibody-mediated CNS disorder. In MRI-negative cases, ¹⁸F-FDG PET may have added value in revealing focal areas of hypo- or hypermetabolism that may support an autoimmune CNS process.

EEG

EEG is essential to establish the presence of temporal neocortical and/or limbic epileptiform discharges as well as slow-wave activity (focal or diffuse, rhythmic or polymorphic, symmetric or asymmetric, theta or delta), demonstrating encephalopathy associated with the psychosis. Specific evidence of extreme delta brush (1-3 Hz slowing with superimposed 20-30 Hz activity) is highly suspicious of NMDAR-Ab-associated pathology, after reasonable exclusion of other etiologies.

Brain biopsy

Brain biopsy should only be considered in selected cases of severe, but potentially treatable, atypical forms of rapidly evolving encephalopathy presenting with refractory psychosis and cognitive decline not associated with known pathogenic neuronal surface autoantibodies, where the diagnosis remains elusive despite exhaustive less invasive diagnostic testing including CSF, EEG and MRI ^{92,93}; biopsy can confirm an inflammatory process, which in this context and after reasonable exclusion of known disorders can indirectly implicate its immunopathogenicity and justify timely immunotherapy trial. Biopsy targets are focal MRI lesions amenable to sampling, or non-dominant, cortico-subcortical, frontal

region in non-lesional MRI to limit the functional impact of potential biopsy-related complications; however, the diagnostic value can be limited by sampling error⁹⁴.

Tumour screening

Serum or CSF positivity for any onconeural antibody (including those neuronal surface autoantibodies associated with tumours) warrants CT scan (or whole body PET) to search for occult malignancy. Abdominal contrast MRI or transvaginal ultrasound should be performed in females with suspected ovarian tumours and testicular ultrasound in males with suspected testicular tumours. Currently, neuronal surface autoantibody seropositivity alone without concurrent autoimmune CNS disorder is not known to have paraneoplastic associations.

Treatment strategies

Symptomatic approaches to psychiatric management

AE-related psychiatric symptoms including confusion, psychosis, or agitation can prove difficult to manage, especially in a general hospital setting where staff may not have mental health expertise and where the physical environment presents many additional risks. These behavioural problems have led to serious incidents of assaults against staff, or patient suicides on acute medical wards⁴². It is therefore vital to establish appropriate physical environment for treatment. Ideally, this is a secure neuropsychiatric unit staffed with individuals with both physical and mental health nursing expertise, equipped with MRI, EEG, and ability to provide infusion therapies or plasma exchange.

The pharmacological management of psychosis in the acute phase typically involves the use of antipsychotics. However, their use in AE-related psychosis can precipitate autonomic instability, often recognized in the mental health setting as suspected neuroleptic malignant syndrome^{95,96}. Antipsychotics should, therefore, be used with care in those with suspected AP; the general approach of 'start low go slow' is recommended.

There is no clear evidence to support any particular antipsychotic. Antipsychotics that allow an optimal symptom control of psychoses with a minimal risk for extrapyramidal symptoms should be preferentially used, mainly the atypical/second

generation antipsychotics. Moreover, benzodiazepines are essential in the management of catatonia and in unclear cases of psychosis or aggression. Electroconvulsive therapy has been used in some cases for rapid symptom control, with good effects reported ^{97,98}.

Indications for immune treatment

Clear indication for immunotherapy in patients with a psychiatric presentation requires a strength of evidence that is in line with clinical consensus for diagnosis of NMDAR-Ab encephalitis or any other form of AE ¹¹. It is important to note that although the use of immunotherapies in AE is supported by considerable clinical experience, a randomized placebo controlled clinical trial (RCT)-based evidence is currently lacking. Based on the existing evidence we suggest that immunotherapy can be *considered* in cases of probable or definite AP (Box B). To provide a clear indication for immune treatment in AP, there should be both the symptoms and paraclinical features supportive of a probable AP diagnosis and the presence of IgG class anti-neuronal antibodies in CSF.

In some cases of AE, such as LGI1 antibody-associated disease, CSF antibodies may be undetectable. Since these antibodies are less frequently associated with psychosis, a case of AP associated with LGI1 antibodies, for example, might only be able to achieve 'probable' AP status.

For patients with organic psychosis that does not satisfy the high threshold for a definite AP diagnosis, the presence of clear diagnostic abnormalities such as inflammatory changes in CSF or characteristic EEG and/or MRI abnormalities as described above should prompt careful consideration of immunotherapy after reasonable exclusion of alternative etiologies. Lumbar puncture is not always possible, particularly in acutely psychotic patients, and 'barriers' to lumbar puncture may exist that reflect cultural differences between psychiatric and neurological practices. In these cases, IgG neuronal surface autoantibody seropositivity coupled with one other item of positive paraclinical evidence *must* be present to support a probable AP diagnosis and justify an immunotherapy trial. In all cases, the potentially psychosis-exacerbating effects of high dose steroid treatment, as just one element of the significant adverse effect profiles of most immunotherapies, must be carefully balanced against the possible immunotherapy benefits.

In cases where supportive investigations are normal or unavailable, particularly if the neuronal autoantibody seropositivity is the sole abnormality, it is far from clear whether immunotherapy has a role. To extrapolate from the literature on treatment of AE to treatment of such individuals would be dangerous and *is not recommended*. There are only limited, unblinded case series to suggest that patients with serum-only NMDAR-Abs and psychosis do respond to treatment with immunotherapy, rather than antipsychotics ^{54,99}. The number of immunotherapy-treated serum-only cases reported is considerably fewer than the number reported who have CSF antibodies. There is currently a phase II randomized controlled trial underway to compare intravenous immunoglobulins (IVIG) and rituximab with placebo in this group (SINAPPS-2: see ¹⁰⁰). Presently, treatment consideration for this group should be undertaken on a case by case basis, following evaluation by an expert team of neurologists and psychiatrists, with specialist technical neuroimmunology input where appropriate. Rheumatologists or others with specific experience in immunotherapies can also be very helpful.

Panel of treatment options

The clinical consensus on AE treatment strategies involves the rapid initiation of treatment to remove circulating antibodies including either tumor removal, if relevant, or plasma exchange/immunoadsorption or IVIG, followed by immunosuppression to suppress antibody synthesis, with either steroids or steroid-sparing agents, such as azathioprine, methotrexate or mycophenolate mofetil. The rapid progression to second line treatments such as rituximab, which depletes CD20-positive B cells, or cyclophosphamide is also common practice. In some centers, rituximab is used first line. This treatment approach appears to provide the best outcomes when started within the first few weeks of symptoms ¹⁰¹⁻¹⁰³, with fewer relapses in those with second line immunotherapy ¹⁰¹. However, as noted above, none of these approaches have been evaluated in RCTs, even though they are now part of current guidelines for treatment of AE.

There is no evidence that ongoing treatment with antipsychotics can prevent AP relapse. Further, once a patient with definite AP or AE has been treated effectively with immunotherapy, antipsychotic or any other symptomatic treatments can be cautiously tapered off, while remaining vigilant for potential re-emergence of

psychotic symptoms (since post-encephalitic patients continue at risk of *de novo* psychotic disorder ¹⁰⁴).

Ethical issues and perspectives

The ethical issues regarding the treatment of these patients primarily revolve around the question of whether a trial of immunotherapy is warranted in patients where the diagnosis of AP is uncertain, but considered likely. Currently, there are no trials to address this issue and most data available is in the form of case reports and series. Clearly, well-conducted trials are needed to inform treatment options, but these are somewhat hampered by the current lack of consistency of the diagnostic approach. Therefore, we recommend that trials in appropriate patients, with defined diagnostic categories as presented here, designed to confirm or reject immunotherapeutic approaches, should be established (eg. the SINAPPS-2 study:

<https://clinicaltrials.gov/ct2/show/NCT03194815>).

Another important aspect to consider in the future will be whether patients with a definite or probable AP who refuse treatments should be treated coercively under country-specific mental health law, so that appropriate immunotherapies can be attempted. Whereas treatment of incapacitous patients with severe AE is commonplace, compulsory immunotherapy of patients with a possible or probable autoimmune psychosis may cause concern for many patients, relatives and clinicians, and would require a comprehensive clinical and ethical analysis of the risks and possible benefits of both the immunotherapy and treatment as usual (antipsychotics or watch and wait). In doing so, the patient's advance directive or, if such is not available or applicable, the presumed will of the patient must be observed.

Conclusions and future directions

We have summarized an approach to the diagnosis and management of psychosis of probable autoimmune origin, highlighting its inherent diagnostic challenges. It is currently unknown which proportion of patients with an acute-onset psychosis and red flag symptoms has an autoimmune brain disease, because they are not routinely

investigated. We should therefore prioritise the implementation of current best practice in neuroimaging, neurophysiology, and neuroimmunological testing of CSF, to identify the proportion of patients who require a different treatment approach, immunotherapy. A similar approach to the diagnosis of AE ¹¹ has been validated ^{105,106} and an immunotherapy response in suspected autoimmune epilepsy has been established ^{103,107}. We hope that the current criteria will stimulate parallel efforts to validate the existence of AP and begin to document the response to immunotherapy. It is also essential that the outcome of treatment in these cases is shared with the clinical community, for instance through the GENERATE-psych database ¹⁰⁸.

Lastly, more research is required to address the current diagnostic and therapeutic pitfalls in evaluating autoimmune psychosis in clinical practice. There is preliminary evidence that the epitopes targeted by NMDAR-Abs are different in AP ⁵² and research to demonstrate and recognise these antibodies may help in better selection of those with a predominantly psychotic presentation. The developments summarized here will be essential for designing multi-center randomized clinical trials aimed at assessing the efficacy of targeted immunotherapies.

Box A:

Aims of the current consensus paper:

1. Summarise the reasons for thinking that some forms of psychosis are autoimmune
2. Describe briefly autoimmune encephalitis (AE) and discuss whether existing studies of AE support the existence of autoimmune psychosis (AP)
3. Propose the future approach to the investigation of possible AP
4. Summarise the possible immunotherapies that will help define AP.
5. Overall, ensure that psychiatrists think about AP or AE in clinical practice so that neurological referral/appropriate immunotherapies are considered
6. Ensure that systematic studies are undertaken on such cases for future validation and design of clinical trials

BOX B:**Proposed diagnostic criteria for autoimmune psychosis (AP)**

For a diagnosis of possible AP the patient must be currently psychotic with abrupt onset (rapid progression of less than 3 months) of psychotic symptoms with at least one of the following:

- 1) recent or current tumour,
- 2) movement disorder (catatonia or dyskinesia),
- 3) adverse response to antipsychotics raising suspicion of neuroleptic malignant syndrome (rigidity, hyperthermia or raised CK),
- 4) severe or disproportionate cognitive dysfunction,
- 5) decreased conscious level,
- 6) seizures not explained by a previously known seizure disorder
- 7) significant autonomic dysfunction (abnormal or unexpectedly fluctuant blood pressure, temperature or heart rate).

If a patient has possible AP, they should be investigated as per section 5, including EEG, MRI, serum autoantibodies and CSF analysis (including CSF autoantibodies). The results should either lead to a non-AP or probable AP diagnosis.

For a diagnosis of probable AP the patient must be currently psychotic with abrupt onset (rapid progression of less than 3 months) of psychotic symptoms, and at least one of the following:

- 1) to 7) as above.

With at least one of the following:

- 1) CSF pleocytosis of more than five WBCs per mm³
- 2) Bilateral brain abnormalities on T2-weighted fluid-attenuated inversion recovery MRI highly restricted to the medial temporal lobes

Or two of the following:

- 3) EEG encephalopathic changes (i.e. spikes, spike-wave activity or rhythmic slowing (IRDA, IRTA activity) or focal changes or extreme delta brush
- 4) CSF oligoclonal bands and/or increased IgG index.
- 5) The presence of a serum anti-neuronal antibody detected by cell-based assay.

After exclusion of alternative diagnoses.

A diagnosis of **definite AP** requires that the patient meets the criteria for probable AP with IgG class anti-neuronal antibodies in CSF.

Box C:

Red flags for suspicion of AE in patients with psychosis (after ^{9,62}). See Box B for those criteria required for a diagnosis of AP.

Infectious prodrome

New-onset severe headache or significant change in headache pattern

Rapid progression

Adverse response to anti-psychotics/malignant neuroleptic syndrome

Lack of response to anti-psychotics

Movement disorder (catatonia or dyskinesia)

Focal neurological disease

Decreased consciousness

Autonomic disturbance

Aphasia, mutism or dysarthria

Seizures

Presence of recent or current tumour

Hyponatraemia (not explained by side effects of medication, e.g., SSRIs, carbamazepine and others)

Other autoimmune disorders

Paraesthesia

Box D:**Search strategy:**

Relevant papers were identified through PubMed searches of articles published in English up to Oct 1st, 2018, using the search terms (alone or in combination): “autoimmune encephalitis”, “limbic encephalitis”, “anti-NMDA receptor encephalitis”, “autoimmune psychosis”, “antibody-mediated psychosis”, “mild encephalitis”, “neuronal surface antibodies” and “neuronal autoantibodies”. Additional studies were identified from the authors’ files. The final reference list was generated on the basis of relevance to the topics covered in this Position Paper.

Table 1. Evidence linking inflammation, immune dysregulation and autoimmunity to psychotic disorders and autoimmune encephalitis

	Schizophrenia and psychotic disorders	Autoimmune encephalitis
Immunogenetic associations	<p>Strong and diffuse association at the MHC locus ¹⁶; causal HLA variants have proved elusive; the association may arise in part due to structurally diverse alleles of the complement component 4 (C4) genes ¹⁷.</p> <p>Associations also strongly enriched among genes that are expressed in tissues with important immune functions, particularly B-lymphocyte lineages (CD19 and CD20) ¹⁶</p>	<p>LGI1 encephalitis most strongly associated with HLA-DRB1*07:01 ^{109,110}; also HLA-DR7 and HLA-DRB4¹¹¹.</p> <p>CASPR2 antibodies less strongly associated with HLA-DRB1*11:01 ¹⁰⁹.</p> <p>NMDAR encephalitis weakly associated with HLA-I allele B*07:02 ¹¹⁰.</p>
Autoimmunity in subject and/or first degree relatives of psychosis	<p>Presence of autoimmune disease increases the risk of psychosis and vice versa ^{20-22,112,113}.</p> <p>A family history of autoimmunity increases risk of psychoses by 10% and a family history with psychosis increases the risk of autoimmune diseases by 6% ¹⁹</p>	Variable autoimmunity in patient and family.
Serum biomarkers	<p>Raised CRP, IL-6, IL-1 beta and TGF-alpha increased in acute psychosis compared to HCs ²³; raised IL-12, IFN-gamma, TNF-alpha and sIL-2R may be trait markers ²³.</p> <p>Reports of increased prevalence of multiple neuronal or non-neuronal antibodies versus controls ¹¹⁴ (although this review conflated multiple assay methodologies and positivity thresholds, often with small sample sizes in included studies).</p> <p>Reports of increased prevalence of NMDAR-Abs may be dependent on assay used ^{37,38}.</p>	<p>Antibodies to neuronal surface antigens, particularly NMDAR ²⁸.</p> <p>No consistent cytokine/chemokine abnormalities in peripheral blood ¹¹⁵; elevated Th17 pathway markers may help differentiate AE with antibodies to neuronal surface antigens ¹¹⁶.</p>
CSF biomarkers	Increased CSF/serum albumin ratio, CSF protein, IgG ratio, IL-6 and IL-8 in psychosis compared to HC ¹ .	Pleocytosis frequent, specific antibodies usually present, intrathecal antibody synthesis in most cases ^{28,57,118} . NMDAR encephalitis

	<p>Pleocytosis between 3 and 10% ^{50,51,117}, CSF-restricted OCBs (7 - 15%) ^{50,51} and elevated neopterin (34%) ¹¹⁷.</p>	<p>characterised by few but frequent NR1-specific intrathecal B cells ⁴⁹</p> <p>CSF TNF-alpha, IL-6, IL-10, IFN-gamma, IL-17A and CXCL13 elevated in NMDAR encephalitis ^{115,119,120}.</p> <p>Elevated neopterin common in NMDAR encephalitis ¹¹⁹.</p>
Infectious antecedents	<p>Psychosis risk increased by specific viral and protozoal infections during pregnancy ¹²¹, childhood ¹²² or adulthood ^{123,124}.</p> <p>Cumulative effect of multiple infections on psychosis risk ^{20,113}.</p> <p>Psychosis diagnosis shows temporal relationship with preceding infectious episode such that risk is increased nearer the time of infection ¹²⁵.</p>	<p>Strong association between NMDAR encephalitis and preceding or concurrent HSV encephalitis in a proportion of patients ^{71,126}. Also associated with nonencephalitic HSV-1 infection ¹²⁷.</p> <p>Other viral organisms (mainly herpesviruses) also implicated in multiple AE subtypes ¹²⁸.</p> <p>HSV encephalitis also associated with production of NMDAR-Abs without resulting secondary encephalitis ¹²⁹.</p>
Immunopathology	<p>Marked variability in studies but evidence of increased microglial activation ⁴ and density ⁵, SERPINA3 and IFITM expression ⁴.</p> <p>Meta-analytical evidence of increased expression of pro-inflammatory genes at the protein and transcript level ⁵.</p> <p>In limited, small studies, lymphocyte infiltration in 20% of post-mortem schizophrenia brains particularly in hippocampus ^{26,27}.</p>	<p>High CD8/CD3 T cell infiltrates in patients with paraneoplastic or GAD-Ab related conditions ¹³⁰.</p> <p>Neuronal loss and complement activation in LGI1-Ab encephalitis ¹³¹.</p> <p>Minimal neuronal loss or complement deposits and variable cellular infiltrates in NMDAR-Ab encephalitis ¹³¹⁻¹³³.</p>

Table 2. Summary of main antigenic targets in autoimmune encephalitis, with associated psychiatric features (adapted with permission from Pollak et al., 2018). Note that it is not recommended to screen for all these antibodies in patients with an isolated psychotic presentation (see section 5).

Antigen	Antigen description/epitope	Main encephalopathy syndrome; which psychiatric features?	Other associated neurological disorders	Main psychiatric features
COMMONLY TARGETED ANTIGENS				
NMDAR	Ligand gated ion channel	Encephalopathy (frequently extralimbic manifestation).	Post-herpes simplex encephalitis relapse with chorea; paediatric dyskinetic encephalitis lethargica; idiopathic epilepsy; immunotherapy-responsive dementia ^{71,126,134-136} .	Anxiety, agitation, bizarre behaviour, catatonia, delusional or paranoid thoughts, and visual or auditory hallucinations. Also movement disorder, seizures, autonomic instability ^{34,57,101} .
LG11*	VGKC- and AMPAR-associated secreted molecule	LE with or without faciobrachial dystonic seizures; prominent hyponatraemia.	Morvan's syndrome, NMT, epilepsy, REM sleep behaviour disorder ¹¹⁸ . Rarely isolated movement disorder (parkinsonism, dystonia, chorea) ^{137,138} .	Confusion, hallucinations, depression ¹¹⁸ .
CASPR2*	VGKC-associated adhesion molecule	Morvan's syndrome: peripheral nerve hyperexcitability, autonomic instability, encephalopathy.	LE, NMT, epilepsy ¹¹⁸ . Rarely isolated movement disorder (chorea, myoclonus) ^{139,140} .	Confusion, hallucinations, agitation, delusions ¹⁴¹ .
AMPAR	Ligand gated ion channel	LE	n/a	Personality change, psychosis, apathy, agitation, confabulation ¹⁴²⁻¹⁴⁴ .
GABA _A R	Ligand gated ion channel	LE with refractory seizures	Varied presentations ¹⁴⁵	Confusion, anxiety, affective changes (inc depression), hallucinations, catatonia ¹⁴⁵⁻¹⁴⁷ .

GABA _B R	Ligand gated ion channel	LE with refractory status epilepticus	Opsoclonus-myoclonus; cerebellar ataxia; PERM ^{148,149}	Psychosis, agitation, catatonia ^{142,148} .
Hu	Intracellular RNA-binding protein	LE or limbic encephalomyelitis occurring with small cell lung cancer.	Painful sensory neuropathy; cerebellar ataxia ^{150,151} .	Confusion, depression, less commonly hallucinations ^{150,151} .
Ma2	Intracellular protein involved in mRNA processing or biogenesis	LE occurring with testicular germ cell tumours; REM sleep disorder is common; frequent short-term memory problems.	Visual dysfunction, gait disturbance, hypokinesia ^{152,153} .	Confusion and anxiety including obsessions and compulsions ^{152,153} .
CRMP5/CV2	Intracellular protein involved in axon guidance	LE occurring with small cell lung cancer or thymoma.	Chorea; sensory neuropathy ¹⁵⁴ .	Subacute dementia; also personality change, depression, confusion and psychosis ¹⁵⁴ .
Amphiphysin	Intracellular	Stiff person syndrome.		Rarely can present with depression and anxiety, psychosis ^{155,156} .
LESS COMMONLY TARGETED ANTIGENS OR THOSE MORE RECENTLY DESCRIBED				
D2R	Metabotropic receptor	'Basal ganglia encephalitis' with prominent movement disorder (dystonia, parkinsonism, chorea, tics) ¹⁵⁷	SC, PANDAS ¹⁵⁸ .	Agitation, depression, psychosis, emotional lability. ¹⁵⁸
DPPX	Auxiliary subunit of Kv4.2 potassium channels	LE with enteropathy	PERM ¹⁵⁹	Amnesia, delirium, psychosis, depression ^{160,161} .

MGlur5	Metabotropic glutamate receptor.	'Ophelia syndrome': LE in association with Hodgkin lymphoma.	Paraneoplastic LE without lymphoma, or nonparaneoplastic LE ¹⁶² . Immunotherapy-responsive prosopagnosia ¹⁶³ .	Depression, anxiety, delusions, visual and auditory hallucinations, personality change, anterograde amnesia ^{162,164} .
IgLON5	Neural cell adhesion molecule of unclear function.	Characteristic sleep disorder preceded or accompanied by bulbar symptoms, gait abnormalities, oculomotor problems and cognitive decline; a tauopathy, strongly associated with HLA-DRB1*10:01. ^{165,166}		Usually chronic cognitive decline, sometimes frank dementia ^{165,166} .
Neurexin 3 α	Synaptic molecule involved in formation and maturation of synapses.	Infectious-like prodrome followed by cognitive dysfunction, seizures, reduced consciousness, and orofacial dyskinesias; sometimes severe clinical course; mimic of NMDARE but with less prominent psychiatric symptoms ¹⁶⁷ .		Agitation, emotional lability and confusion ^{167,168} .
ARHGAP26	A multidomain protein involved in regulation of endocytosis.	Autoimmune cerebellar ataxia with dizziness and dysarthria; also memory dysfunction and depression ^{169,170} .		One patient reported with immunotherapy-responsive psychosis with suicidality, aggression, mutism ¹⁷¹ .
Synapsin	A synaptic vesicle-associated protein involved in regulation of neurotransmitter release.	69-year-old man with confusion, disorientation, seizures, and left hippocampal hyperintensities on MRI ¹⁷² .	Synapsin IgG also found in patients with neurological and psychiatric disorders (including psychosis, depression and bipolar disorder).with unclear pathogenic significance ¹⁷³ .	

AK5	An intracellular (cytosolic) nucleoside monophosphate kinase, expressed exclusively in the brain.	>50 yo; subacute pure anterograde amnesia, occurring in most cases after a prodromal phase of asthenia, anorexia, and depression. Hippocampal atrophy on MRI. Seizures not reported ¹⁷⁴ .		Prodromal depression, prominent anxiety. Rarely delusions ^{174,175} .
GFAP	An intracellular (cytosolic) glial intermediate filament protein.	Corticosteroid-responsive meningoencephalitis or encephalitis, with or without myelitis. Presents with subacute onset of memory loss and confusion. ¹⁷⁶⁻¹⁷⁸		Occur in 29% in one study but not described in detail ¹⁷⁶ . Psychosis and 'behavioural changes' reported ¹⁷⁹ .

AK5: adenylate kinase 5; ARHGAP26: Rho GTPase activating protein 26; ATD: amino terminal domain; BPAD: bipolar affective disorder; CBA: cell-based assay; ELISA: enzyme-linked immunosorbent assay; GFAP: glial fibrillary acidic protein; LE: limbic encephalitis; MDD: major depressive disorder; NMT: neuromyotonia; PERM: progressive encephalomyelitis with rigidity and myoclonus; RIA: radioimmunoassay; SC: Sydenham's chorea; PANDAS: paediatric autoimmune neuropsychiatric disorders associated with Streptococcal infections *Note that VGKC antibodies measured by radioimmunoprecipitation are not recommended as the LGI1 and CASPR2 cell based assays are more reliable.

Figure 1: Magnetic resonance imaging (MRI) and fluorodeoxyglucose positron emission tomography (FDG-PET) findings of a 31 year old female patient with a catatonic syndrome which initially presented with affective changes, delusions, agitation and delirium-like episodes. Initial CSF analysis revealed elevated CSF WBCs and protein. Following non-response to anti-infective agents for presumed viral encephalitis, she received a diagnosis of catatonic schizophrenia. After 21 months, the diagnosis of NMDAR-Ab encephalitis was made following screening for neuronal autoantibodies, and MRI and FDG-PET was performed. The MRI is largely unremarkable except for a moderate perisylvic and temporal brain atrophy, and slight periventricular hyperintensities. Both hippocampi are normal. The FDG-PET showed a cortical hypometabolism pronounced on the left hemisphere. Cerebellar hypometabolism was particularly prominent on the right side (probably due to crossed cerebellar diaschisis; adapted with kind permission from ¹⁸⁰).

Figure 2: Extreme delta brush (EDB)-like EEG pattern in NMDAR-Ab encephalitis. The patient was a 27 year old female who had been diagnosed with schizophrenia two years previously, following a first episode of psychosis. During the course of a research study using stored samples, serum NMDAR IgG at titre 1:1000 were detected in blood taken during this first episode as well as during a second episode two years later when the patient presented with catatonia. At this time CSF NMDAR IgG was also detectable at titre 1:320, and the patient had a lymphocytic pleocytosis (21 cells/ul) with unmatched oligoclonal bands. At this point her EEG showed intermittent bilateral delta activity with superimposed fast activity, a pattern subsequently recognised as an EDB-like pattern (note the abnormality is less widespread than in classical descriptions of EDB). Despite the purely psychiatric presentation, the patient was rediagnosed post-hoc as suffering from NMDAR-Ab encephalitis. The case was originally described in ⁷⁸.

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Appendix

Authors present at the round table sessions at the 14th Psychoimmunology Expert Meeting (<http://www.psychoimmunology-experts.de/>) at Günzburg, Germany, in March 2018:

Thomas A. Pollak

Belinda Lennox

Sabine Müller

Michael E. Benros

Harald Prüss

Ludger Tebartz van Elst

Hans Klein

Johann Steiner

Thomas Frodl

Bernhard Bogerts

Li Tian

Dominique Endres

Ebrahim Haroon

Robert Yolken

Francesco Benedetti

Angelos Halaris

Jeff Meyer

Hans Stassen

David A Brown

Angela Vincent

Souhel Najjar

Karl Bechter

Authors not present at the round table sessions:

Laurent Groc

Marion Leboyer

Dietmar Fuchs

Alkomiet Hasan

Bernhard T. Baune

Markus Otto