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# Neuroimmune-mediated neuropsychiatric syndromes: perspectives for standardised diagnostics and personalised care

Elizabeth M. Scott[1], Mirim Shin[1], Richard B. Banati[1,2,4], David A. Brown[3,4,5], Dagmar Koethe[1], F. Markus Leweke[1,7], Cathrin Rohleder[1,6,7] and Ian B. Hickie[1]

[1]Brain and Mind Centre, The University of Sydney, Sydney, NSW, Australia; [2]Australian Nuclear Science and Technology Organisation (ANSTO), Lucas Heights, NSW, Australia; [3]The Westmead Institute for Medical Research, Westmead, NSW, Australia; [4]Faculty of Medicine and Health, Sydney Medical School, The University of Sydney, Sydney, NSW, Australia; [5]Department of Clinical Immunology and Immunopathology, Institute of Clinical Pathology and Medical Research, NSW Health Pathology, Westmead Hospital, Westmead, NSW, Australia; [6]Endosane Pharmaceuticals GmbH, Berlin, Germany and [7]Central Institute of Mental Health, Department of Psychiatry and Psychotherapy, Medical Faculty Mannheim, Heidelberg University, Mannheim, Germany

## Abstract

There is considerable interest in the role of neuroimmune processes in neuropsychiatric presentations among young people seeking mental health, neurological, paediatric and rheumatological services. The increasing availability of new immunotherapies, particularly monoclonal antibodies, introduces challenges in effectively and appropriately selecting candidates for immunotherapies. Neuroimmune-mediated neuropsychiatric syndromes (NIMNPS) typically include two broad types: i) 'autoimmune encephalitis', characterised by acute or subacute onset, neurological signs such as seizures, delirium or motor features and severe psychotic or major mood phenomena. Anti-N-methyl-D-aspartate receptor encephalitis was a pioneering clinical example, but various other autoantibodies have since been associated with this phenotype; and ii) atypical mood or psychotic syndromes with sub-acute or insidious onset, moderately severe atypical mood or psychotic symptoms, autonomic dysregulation, narcolepsy-like features, poor response to conventional treatments and adverse (notably motor) effects from psychotropic medications. Diagnosis of NIMNPS requires clinical or laboratory evidence of direct brain involvement, though autoantibodies are not always detectable. Given the broad and controversial diagnostic criteria for NIMNPS, we propose standardised clinical criteria for identifying 'possible cases', followed by laboratory, neuropsychological and brain imaging tests to confirm 'probable' cases suitable for immunotherapy. We emphasise rapid clinical and informed co-decision-making with young people and their families and loved ones. While immunotherapy holds promise for symptom alleviation, highly-personalised approaches and long-term management are essential. Future research should validate our proposed criteria, establish optimal, standardised yet personalised immunotherapy strategies that balance between clinical benefit and risks, and identify predictive markers of treatment response.

## Impact Paper

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**Corresponding author:**
Cathrin Rohleder;
Email: cathrin.rohleder@sydney.edu.au

## Introduction

Recent research has vigorously explored the pathophysiological implications of neuroimmune processes and specific neuronal antibodies across mental, neurological, paediatric and rheumatological disorders, with a particular focus on atypical and early-onset mood or psychotic syndromes (Leypoldt et al. 2015; Newman et al. 2016; Al-Diwani et al. 2017; Fukata et al. 2018; Pollak et al. 2018; Pape et al. 2019). A pioneering clinical example is anti-*N*-methyl-D-aspartate receptor (NMDAR) encephalitis, caused by specific autoantibodies to NMDAR (Dalmau et al. 2007; Dalmau et al. 2011). Initially, anti-NMDAR encephalitis was described as a neuropsychiatric syndrome that progressed from a prodromal phase with non-specific symptoms to psychosis, memory deficits, seizures and language disintegration, to a catastrophic state of unresponsiveness with catatonic features (Dalmau et al. 2011; Ramanathan et al. 2014). Subsequent research has shown that NMDAR autoantibodies are associated with a much broader, often sub-acute, non-specific clinical phenotype, including not only psychotic phenomena and catatonia, but also a wide spectrum of mood disturbance, aggression and sleep disturbances (Ramanathan et al. 2014; Warren et al. 2018; Al-Diwani et al. 2019).

In recent years, the identification of various neuronal surface antibodies (NSAbs) implicated in 'neuronal surface antibody syndromes' (NSAS) associated with mood and psychotic disorders has expanded (Zuliani et al. 2012; Ramanathan et al. 2014; Pollak et al. 2016). These NSAbs include antibodies to voltage-gated potassium channel complex

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**Table 1.** Psychiatric and clinical features of common types of autoantibodies

| Antigen | Psychiatric symptoms | Other clinical characteristics |
|---|---|---|
| **Neuronal surface autoantibodies** | | |
| **NMDAR** | Psychosis, schizophreniform illness, catatonia, hallucinations, aggression | Seizures, amnesia, movement disorder, autonomic instability, speech dysfunction, decreased consciousness |
| **LGI1 (VGKC)** | Amnesia, confusion, hallucinations, memory deficits, depression, sleep disorders, rapidly progressive dementia | Limbic encephalitis with or without faciobrachial dystonic seizures, hyponatremia, myoclonus, |
| **CASPR2 (VGKC)** | Insomnia, panic attacks, confusion, schizophreniform illness, depression | Morvan's syndrome, neuromyotonia, muscle spasms, fasciculations, limbic encephalitis (less common) |
| **AMPAR** | Confusion, personality change, psychosis, apathy, agitation, confabulation | Limbic encephalitis |
| **$GABA_AR$** | Confusion, affective changes (including depression), hallucinations | Limbic encephalitis, seizures |
| **$GABA_BR$** | Psychosis, agitation, catatonia | Refractory seizures, status epilepticus |
| **GlyR** | Behavioural changes, schizophreniform syndrome | PERM, limbic encephalitis, stiff person syndrome, hyperekplexia |
| **D2R** | Agitation, depression, psychosis, emotional lability, mutism, sleep disturbance, reduced consciousness | Basal ganglia encephalitis, movement disorders (dystonia, parkinsonism, chorea, ocular flutter, motor tics) |
| **DPPX** | Amnesia, psychosis, depression, agitation | Encephalitis, CNS hyperexcitability, hyperekplexia, movement disorders (tremor), seizures, PERM |
| **mGluR5** | Behavioural changes, emotional instability, depression, anxiety, delusions, visual and auditory hallucinations, memory deficits, anterograde amnesia | Limbic encephalitis (Ophelia syndrome), myoclonus |
| **IgLON5** | Chronic cognitive decline | Sleep disorder, gait abnormalities, oculomotor problems |
| **Neurexin 3$\alpha$** | Agitation, emotional lability, confusion | Cognitive dysfunction, seizures, reduced consciousness, and orofacial dyskinesias, mimic NMDARE |
| **Other CNS autoantibodies** | | |
| **GAD** | Associated with psychosis | Limbic encephalitis, type 1 diabetes mellitus, stiff person syndrome, temporal lobe epilepsy, cerebellar ataxia |
| **Hu** | Confusion, depression, anxiety, less commonly hallucinations | Limbic encephalitis or limbic encephalomyelitis |
| **Ma2** | Confusion and anxiety, including obsessions and compulsions | Limbic encephalitis, REM sleep disorder, short-term memory problems |
| **CRMP5 (CV2)** | Depression, confusion, psychosis | Limbic encephalitis |
| **Amphiphysin** | Depression, anxiety, psychosis | Stiff person syndrome |
| **GFAP** | Psychosis, behavioural changes | Meningoencephalitis, encephalitis, with or without myelitis, memory loss and confusion |
| **ARHGAP26 (GRAF)** | Psychosis, suicidality, aggression, mutism, depression | Autoimmune cerebellar ataxia with dizziness and dysarthria, memory dysfunction |
| **AK5** | Prodromal depression, anxiety, rarely delusions | Anterograde amnesia, anorexia, hippocampal atrophy |
| **Synapsin** | Psychosis, depression, bipolar disorder | Disorientation, seizures |
| **Systemic non-CNS autoantibodies** | | |
| **ANA** | Psychosis | Systemic lupus erythematosus |
| **TG/TPO** | Depression, anxiety, psychosis | Thyroiditis, Hashimoto's encephalopathy |

*Abbreviations*: AK5, adenylate kinase 5; AMPAR, α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor; ANA, antinuclear antibody; ARHGAP26, antibody raised against Rho GTPase activating protein 26; CASPR2, contactin-associated protein-like 2; D2R, dopamine 2 receptor; DPPX, dipeptidyl-peptidase-like protein-6; GABAAR, α-aminobutyric acid receptor type A; GABABR, α-aminobutyric acid receptor type B; GAD, glutamic acid decarboxylase; GFAP, glial fibrillary acidic protein; GlyR, glycine receptor; LGI1, leucine-rich glioma inactivated 1; mGluR5, metabotropic glutamate receptor 5; NMDAR, N-methyl-D-aspartate receptor; NMDARE, anti-N-methyl-d-aspartate receptor encephalitis; PERM, progressive encephalomyelitis with rigidity and myoclonus; REM, rapid eye movement; TG, thyroglobulin; TPO, thyroid peroxidase; VGKC, voltage-gated potassium channel complex.

associated molecules LGI1 (leucine-rich glioma inactivated 1) and contactin-associated protein 2, α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor, γ-aminobutyric acid receptor types A and B ($GABA_AR$, $GABA_BR$), glycine receptor, dopamine D2 receptor (D2R), dipeptidyl-peptidase-like protein-6, metabotropic glutamate receptor 5, IgLON5 and neurexin 3α (Zuliani et al. 2012; Ramanathan et al. 2014; Pollak et al. 2016; Herken and Pruss 2017; Endres et al. 2020a; Prüss 2021; Patel et al. 2022; Endres et al. 2022a). These non-NMDA NSAS are also characterised by an acute or subacute onset, a wide range of psychiatric symptoms, cognitive impairment and specific neurological manifestations such as seizures, movement disorders and autonomic dysfunction (Zuliani et al. 2012; Pollak et al. 2016; Herken and Pruss 2017; Endres et al. 2020a; Patel et al. 2022; Endres et al. 2022a). Table 1 summarises key NSAbs with their associated psychotic or other clinical characteristics.

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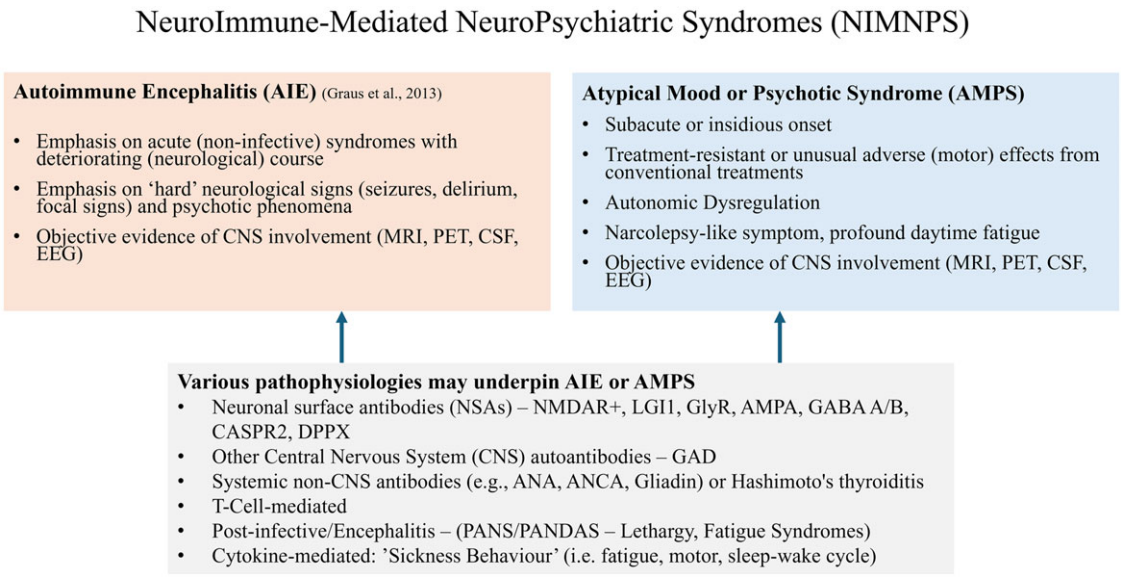


**Figure 1.** Schematic illustration elucidating neuroimmune-mediated neuropsychiatric syndromes.

In addition to NSAbs, other central nervous system (CNS) autoantibodies (e.g., glutamic acid decarboxylase) and systemic non-CNS autoantibodies (e.g., antinuclear antibody [ANA], thyroperoxidase and thyroglobulin) have been associated with neuropsychiatric manifestations (Grain et al. 2017; Pollak et al. 2018; Siegmann et al. 2018; Cullen et al. 2019). A subset of patients with systemic autoimmune disorders, including connective tissue disorders (e.g., systemic lupus erythematosus characterised by ANA production) as well as rheumatoid arthritis and thyroid disease (e.g., Hashimoto's thyroiditis, and Grave's disease), develop neuropsychiatric symptoms such as cognitive changes, mood and anxiety disorders, symptoms of confusion and psychosis (Jeltsch-David and Muller 2014; Endres et al. 2016; Pollak et al. 2018; Siegmann et al. 2018; Cullen et al. 2019; Li and Li 2019; Pisetsky 2020).

Key CNS and non-CNS autoantibodies and their associated psychotic or other clinical characteristics are listed in Table 1 (Gresa-Arribas et al. 2016; Dalmau and Graus 2022). However, the list of potential autoantibodies linked to neuropsychiatric manifestations is continuously growing.

International criteria for the clinical diagnosis of autoimmune encephalitis (AIE) (Graus et al. 2016) in acute paediatric settings provided a template for rapid clinical decision-making and personalised immunotherapies. This clinically orientated approach, along with informed co-decision-making involving young people and their families, appropriately addresses the acute healthcare needs of those affected. Following the anti-NMDAR experience, a similar approach was proposed for AIE associated with major psychotic syndromes and the concept of the autoimmune psychosis was introduced (Endres et al. 2020a; Pollak et al. 2020). However, the paper proposing criteria for 'possible' and 'probable' autoimmune psychosis noted that:

> "*The' criteria for autoimmune psychosis might be too conservative and exclude potential patients with autoimmune psychosis who present with one or more of the following: a more chronic psychotic picture (i.e., >3 months); none of the symptomatic criteria of possible autoimmune psychosis (i.e., no so-called red flags); or normal EEG, MRI, and CSF findings. Establishing that these patients exist and whether they respond to immunotherapies must await future developments.*" (Pollak et al. 2020)

## Classification and terminology of Neuroimmune-Mediated Neuropsychiatric Syndromes (NIMNPS)

Consequently, the broader spectrum of Neuroimmune-Mediated Neuropsychiatric Syndromes (NIMNPS) includes two types of presentations: AIE and 'Atypical Mood or Psychotic Syndromes' (AMPS) (Figure 1). In both AIE and AMPS, while neuronal, CNS or systemic antibodies may underlie the condition, other features may be linked to T-cell activation or cytokine involvement. The NIMNPS are clinically classified as AIE if they exhibit acute or subacute onset, a deteriorating course, prominent psychiatric and neurological features (e.g., seizures, delirium, focal signs), cognitive impairment, autonomic dysfunction and evidence of CNS inflammation (e.g., abnormalities in brain imaging, electroencephalogram (EEG) or cerebrospinal fluid (CSF)), alongside the detection of a brain-specific or other autoantibodies known to be associated with neuropsychiatric syndromes. These cases have attracted the most research attention and active immunotherapy in recent years.

For AMPS cases, the nature of these conditions is often less clear, especially when no specific CNS autoantibodies are detected. They are also less likely to be investigated systematically for direct CNS involvement (i.e., EEG, brain imaging, CSF) and are typically treated principally with psychotropic medications only. However, these syndromes are often characterised not only by atypical mood or psychotic symptoms, but also by autonomic dysregulation, narcolepsy-like symptoms, a subacute or insidious onset, a prolonged or treatment-resistant course and often accompanied by adverse (notably motor) effects from conventional pharmacological treatments (Figure 1). The clinical boundaries of these syndromes and the criteria for both diagnosis and provision of specific immunotherapies remain controversial.

Specific autoimmune disorders, such as NMDAR encephalitis, occur in less than 1% of typical acute psychotic presentations (Lennox et al. 2017; Scott et al. 2018). Given the rarity of these acute syndromes in the general population, specific autoimmune syndromes may occur at the rate of approximately 1 in 10,000 individuals. In contrast, the prevalence of NIMNPS among young people presenting with atypical mood or psychotic disorders may

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be as high as 5-10% (Benros et al. 2014; Endres et al. 2015; Schou et al. 2016; Lennox et al. 2017; Scott et al. 2018; Siegmann et al. 2018).

## Clinical criteria and treatment strategies for Autoimmune Encephalitis (AIE) and NeuroImmune-Mediated NeuroPsychiatric Syndromes (NIMNPS)

A wide range of potentially relevant clinical scenarios is now recognised in young people aged between 12 and 25 years presenting to mental health services, including:

a) Cases presenting with a broad range of atypical psychotic, major mood disorders or mixed syndromes. Therefore, limiting clinical research or potential immunotherapy focus to those with psychotic syndromes is inappropriate;
b) Cases seeking help outside of acute treatment settings; and,
c) Cases who may have a subacute, deteriorating, or more chronic course, with minimal response to conventional psychotropic therapies or very severe neurological side effects from such therapies.

To facilitate the diagnosis and treatment of NIMNPS, our group aimed to define a set of criteria for the phenotype that could be easily implemented in everyday clinical practice and enable a standardised diagnostic process. Based on the clinical scenarios observed in our mental health services and extensive literature review, our research team identified potential phenotype criteria related to illness onset, clinical presentation, disease course and potential further medical and family factors relevant to NIMNPS. These criteria were discussed at several roundtable sessions in 2022. EMS and IBH led further discussions with people experiencing mental health conditions with possible immune involvement and their loved ones. They wrote the concept for this impact paper, which was reviewed and discussed among all co-authors in 2023. Based on the discussion results, CR and MS drafted the manuscript. All co-authors contributed to the working draft, which was circulated regularly and agreed to the final submission.

This consensus process resulted in 12 clinical phenotype criteria for 'possible' cases of NIMNPS (Table 2) that recognise both common scenarios (i.e. AIE and AMPS). These 12 clinical phenotype criteria include 8 core criteria covering clinical features and disease progression – 'course'. 'Possible' cases are defined as those meeting ≥ 3 out of the 8 core criteria, including at least 2 of the 5 'clinical features' and 1 of the 3 'courses' criteria. We recommend that possible cases undergo comprehensive neurological and immunological assessments, including brain imaging (MRI and PET), EEG, CSF, serum laboratory (notably autoantibody) investigations and neuropsychological assessments.

'Probable' cases of NIMNPS are then identified as those who are clinically positive and have evidence of at least two of five objective markers (Table 3). Notably, the presence of autoantibodies in CSF or blood alone is not considered sufficient evidence of a neuroinflammatory process.

The 'probable' case should have the option of receiving highly personalised and sequenced immunotherapy, with a strong emphasis on informed co-decision-making involving young people and their families and loved ones. The sequencing and selection of immunotherapy options (see Table 4) depend on the clinical presentation and results of investigations, such as the identification of specific antibody markers.

**Table 2.** Clinical phenotype criteria for NeuroImmune-Mediated NeuroPsychiatric Syndromes. The 12 clinical phenotype criteria include 8 core criteria, namely five 'clinical features' (criteria 2–6) and three 'course' criteria (criteria 7–9)

| # | Clinical phenotype criteria |
|---|---|
| **Onset** | |
| 1 | Acute (<1 month) or subacute (<3 months) onset of illness episode. |
| **Clinical Features** | |
| 2 | Catatonic symptoms or intermittent agitation and excitatory states, |
| 3 | Major neurological signs, such as seizures or abnormal involuntary movements, |
| 4 | Other major neurological symptoms and signs including severe or persistent headache, marked auto-nomic instability, and severe or persistent central pain syndrome, |
| 5 | Narcolepsy-like episodes or profound sleep-wake cycle perturbations, |
| 6 | Evidence of clinically significant cognitive involvement such as inattention, impairment of memory, disorganisation, inability to comprehend verbal information, reduced verbal expression or mutism. |
| **Course** | |
| 7 | Deteriorating course of illness, including progression of working memory deficits (short-term memory loss), altered mental status, or psychiatric symptoms, |
| 8 | Non-responsive to conventional mood or antipsychotic treatments, |
| 9 | Markedly unusual/unexpected adverse effects of conventional treatments, notably motor and other neurological side effects (e.g., motor tics, severe agitation, akathisia and hyperekplexia). |
| **Other medical or family factors** | |
| 10 | Subclinical or mild overt thyroid disease (usually hypothyroidism), |
| 11 | Personal medical history of prior comorbid autoimmune disorders, |
| 12 | Family History of Major Autoimmune Disorder (1st-degree relative). |

**Table 3.** Characteristics of possible ('clinically-positive') and probable ('laboratory consistent') cases

| | Possible cases | Probable cases |
|---|---|---|
| Clinically positive | ✓ | ✓ |
| Laboratory markers (at least 2 of 5)<br>• Abnormal EEG (focal or diffuse slow or disorganised activity, epileptic activity or extreme delta brush)<br>• MRI abnormalities suggestive of autoimmune encephalitis<br>• Autoantibodies in serum or CSF<br>• Abnormal PET or other nuclear medicine imaging<br>• Abnormal comprehensive neuropsychological testing | ✗ | ✓ |

## Conclusion and perspectives

The prevalence of broadly defined NIMNPS among young people presenting acutely or sub-acutely with atypical mood or psychotic disorders may be as high as 5–10% (Benros et al. 2014; Endres et al.

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2015; Schou et al. 2016; Lennox et al. 2017; Scott et al. 2018; Siegmann et al. 2018). The rapidly emerging evidence of various CNS-specific or systemic immunological abnormalities in these cohorts highlights the urgent need for a comprehensive assessment. It is of paramount importance to determine early in the illness course whether the illness is being driven by neuroimmune processes. Early identification should be coupled with the active consideration of the timely initiation of appropriate immunotherapies (now including new monoclonal antibody therapies) in highly selected cases to optimally manage the disease through early intervention.

Our 12 clinical phenotype criteria provide a standardised approach to diagnosing 'possible' cases of NIMNPS. Drawing from our clinical experience, we have identified 8 of the 12 criteria as core criteria, encompassing clinical features and the disease course. Unlike the diagnostic criteria for autoimmune psychosis proposed by Pollak et al. (2020), our core criteria do not include acute or subacute presentations. This adjustment is based on our observation that also some insidious onset cases show the clinical features and course of possible NIMNPS. This has also been reported by others (Endres et al. 2020b). While acute or subacute onset should be regarded as 'red flags', we believe that an overly conservative approach might miss possible cases of NIMNPS. Therefore, the acute or subacute onset is part of the 12 clinical phenotype criteria but is not considered a core criterion.

'Possible' (i.e., 'clinically-positive') NIMNPS cases should undergo agreed independent investigations to identify individuals who may benefit from a personalised trial of immunotherapy (laboratory consistent 'probable' cases). This diagnostic approach is crucial as AIE and AMPS can be masked by the psychiatric presentation (Moldavski et al. 2021; Endres et al. 2022b), and also medication such as lorazepam may mask epileptiform activity in EEGs (Moldavski et al. 2021). Special attention must be given to those presenting with atypical features of mental illness (Bien et al. 2021; Endres et al. 2022b), as indicated in Figure 1 and represented by our 12 clinical phenotype criteria.

We prioritise rapid clinical decision-making and informed co-decision-making with individuals with NIMNPS and their families and loved ones. However, while there is substantive clinical evidence that immunotherapy for NSAbs can effectively alleviate psychiatric symptoms (Graus et al. 2016; Pollak et al. 2016; Endres et al. 2022b), the role of immunotherapies across the broader spectrum of NIMNPS is yet to be established. Therefore, clinical trials are needed to determine the most appropriate treatment regimens and types for 'probable' cases with non-specific laboratory markers (see Table 4 for our suggestions).

Both specific and non-specific immunotherapies need to be personally tailored, used alongside other conventional therapies, monitored closely (for benefits and adverse effects) and actively managed long-term. In our view, immunotherapy may be warranted in 'probable' NIMNPS cases, where there is clear independent evidence of brain involvement and even in the absence of specific antibodies.

Future research needs to urgently focus on:

i. Broadening clinical screening, particularly within youth-specific mental health services;
ii. Testing the feasibility and validity of our proposed clinical and objective testing criteria for assignation of probable cases;
iii. Conducting systematic evaluation of brain-specific, immune and other laboratory markers and their relationships with demographic, phenotypic, illness course and treatment response (conventional or immunotherapies);
iv. Implementing standardised assessment to evaluate clinical response, functional status and adverse effects (short and long-term) of personalised immunotherapies.
v. Developing optimal, standardised yet personalised immune treatment strategies for NIMNPS, with careful consideration of balancing clinical benefit and potential adverse effects; and,
vi. Identifying clinical and objective predictors of response to various immune therapy options.

**Table 4.** Immunotherapy options depending on the clinical presentation

| Group | Treatment/Intervention |
|---|---|
| Possible Cases:<br>Clinically positive without lab-consistent results | Usual care |
| Probable Cases:<br>Lab-consistent cases without specific autoantibody detected | 1) Steroid-based or steroid-sparing therapies<br>2) Targeted monoclonal therapies (e.g., rituximab) |
| Probable Cases:<br>Lab-consistent cases with specific autoantibody detected | 1) Intravenous immunoglobulins<br>2) Plasma exchange<br>3) Steroid-based or steroid-sparing therapies<br>4) Relevant cancer screening and subsequent intervention |

**Data availability statement.** Data availability is not applicable to this article as no new data were created or analysed in this study.

**Author contributions.** **EMS:** Conceptualisation, Writing – Review & Editing, Funding Acquisition; **MS:** Visualisation, Writing – Review & Editing; **RBB:** Writing – Review & Editing; **DAB:** Writing – Review & Editing; **DK:** Writing – Review & Editing; **FML:** Writing – Review & Editing, **CR:** Visualisation, Writing – Original Draft, Writing – Review & Editing; **IBH:** Conceptualisation, Writing – Review & Editing, Funding Acquisition.

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**Competing interests.** EMS is Principal Research Fellow at the Brain and Mind Centre, The University of Sydney. She is Discipline Leader of Adult Mental Health, School of Medicine, University of Notre Dame and a Consultant Psychiatrist. She was the Medical Director, Young Adult Mental Health Unit, St Vincent's Hospital Darlinghurst until January 2021. She has received honoraria for educational seminars related to the clinical management of depressive disorders supported by Servier, Janssen and Eli-Lilly Pharmaceuticals. She has participated in a national advisory board for the antidepressant compound Pristiq, manufactured by Pfizer. She was the National Coordinator of an antidepressant trial sponsored by Servier. FML is a shareholder of curantis UG (Ltd) and received a research grant from Endosane Pharmaceuticals. CR is a shareholder of lero bioscience UG (Ltd) and is currently employed by Endosane Pharmaceuticals GmbH. IBH is the Co-Director, Health and Policy at the Brain and Mind Centre (BMC) University of Sydney. The BMC operates an early-intervention youth service at Camperdown under contract to headspace. He is the Chief Scientific Advisor to, and a 3.2% equity shareholder in, InnoWell Pty Ltd which aims to transform mental health services through the use of innovative technologies. The remaining authors declare no competing interests.

**Ethical standards.** Ethic Statement is not applicable to this article as no new human data were created or analysed in this study.

## Connections references

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