

evenings and weekends.<sup>11</sup> Many Fortune 500 companies recognise that time for creative work, mindfulness and communication training, team development, and inspired leadership improve the quality of work; here, health-care institutions are behind the times. Distressed physicians avoid seeking help because of stigma, potential career effects, and loss of confidentiality.<sup>3</sup> Peer or professional coaches can help physicians seek support.<sup>12</sup> Licensure regulations requiring that physicians deny any previous mental illness should be eliminated; they do not protect the public and reinforce a culture of secrecy, avoidance, and denial. Every physician has had colleagues, trainees, and personal physicians who died by suicide. Sadly, often it takes a prominent suicide to precipitate improved access to mental health services, mindfulness workshops, and other approaches, yet little meaningful change has occurred in the institutional environments that contribute to the problem. Depression, anxiety, and suicide in physicians is a public health crisis, and Petrie and colleagues' review is a call to action.

\*Ronald M Epstein, Michael R Privitera

University of Rochester School of Medicine and Dentistry,  
Rochester, NY 14642, USA  
ronald\_epstein@urmc.rochester.edu

We declare no competing interests.

- 1 Petrie K, Crawford J, Baker S, et al. Improving the mental health of doctors: a systematic review and meta-analysis of interventions to reduce symptoms of common mental disorders and suicidal ideation in physicians. *Lancet Psychiatry* 2019; published online Feb 7. [http://dx.doi.org/10.1016/S2215-0366\(18\)30509-1](http://dx.doi.org/10.1016/S2215-0366(18)30509-1).
- 2 The National Institute for Occupational Safety and Health. Exposure to Stress: Occupational Hazards in Hospitals. Washington, DC: Centers for Disease Control, 2008.
- 3 Privitera MR. Is burnout a form of depression? It's not that simple. *Medscape Psychiatry*, May 16, 2018. <https://www.medscape.com/viewarticle/896537> (accessed Jan 7, 2019).
- 4 Maslach C, Schaufeli WB, Leiter MP. Job burnout. *Annu Rev Psychol* 2001; **52**: 397-422.
- 5 Maslach C, Leiter MP. New insights into burnout and health care: strategies for improving civility and alleviating burnout. *Med Teach* 2017; **39**: 160-63.
- 6 Dyrbye LN, Thomas MR, Shanafelt TD. Systematic review of depression, anxiety and other indicators of psychologic distress among U.S. and Canadian medical students. *Acad Med* 2006; **81**: 354-73.
- 7 Taylor C, Graham J, Potts HW, Richards MA, Ramirez AJ. Changes in mental health of UK hospital consultants since the mid-1990s. *Lancet* 2005; **366**: 742-44.
- 8 Kendler KS, Thornton LM, Gardner CO. Stressful life events and previous episodes in the etiology of major depression in women: an evaluation of the "kindling" hypothesis. *Am J Psychiatry*. 2000; **157**: 1243-51.
- 9 Segal ZV, Williams JMG, Teasdale JD. Mindfulness-based cognitive therapy for depression: a new approach to preventing relapse. New York, NY: The Guilford Press, 2002.
- 10 Ng JYY, Ntoumanis N, Thøgersen-Ntoumani C, et al. Self-determination theory applied to health contexts: a meta-analysis. *Perspect Psychol Sci* 2012; **7**: 325-40.
- 11 Privitera MR, Atallah F, Dowling F, Gomez-DiCesare C. Physicians' electronic health records use at home, job satisfaction, job stress and burnout. *J Hosp Admin* 2018; **7**: 52-59.
- 12 Hu YY, Fix ML, Hevelone ND, et al. Physicians' needs in coping with emotional stressors: the case for peer support. *Arch Surg* 2012; **147**: 212-17.

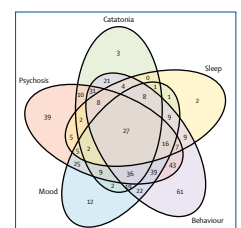
## A transdiagnostic pattern of psychiatric symptoms in autoimmune encephalitis

N-methyl-D-aspartate receptor (NMDAR)-antibody encephalitis is a neuropsychiatric disorder<sup>1,2</sup> that is caused by antibodies against the NR1 subunit of the NMDA receptor. Many patients with NMDAR-antibody encephalitis are first seen by psychiatrists because of the frequent onset of the disease with psychiatric symptoms such as agitation, hallucinations, delusions, or depressed mood. Once the disease progresses, patients typically develop additional neurological symptoms, such as movement disorders, epileptic seizures, autonomic dysfunction, and cognitive deficits.

Diagnosis is established by detection of autoantibodies in serum and CSF, and treatment with first-line (eg, intravenous steroids, plasma exchange) and second-line immunotherapy (eg, rituximab) is usually very effective.<sup>3</sup>

Accumulating evidence highlights the need for an early diagnosis to achieve a good outcome,<sup>4</sup> but antibody testing is often considered only when neurological symptoms begin.<sup>5</sup> To facilitate early treatment, patients with potential NMDAR-antibody encephalitis and psychiatric symptom onset must be identified rapidly to initiate antibody testing of both serum and CSF.

In their systematic review in *The Lancet Psychiatry*, Al-Diwani and colleagues<sup>6</sup> analysed psychiatric symptoms in patients with NMDAR-antibody encephalitis and compared the psychopathological profile to common psychiatric syndromes. Of 1096 records identified in PubMed, 330 satisfied inclusion criteria and described 1100 patients with NMDAR-antibody encephalitis. 464 adult patients with definite NMDAR-antibody



Published Online  
February 11, 2019  
[http://dx.doi.org/10.1016/S2215-0366\(19\)30038-0](http://dx.doi.org/10.1016/S2215-0366(19)30038-0)

See [Articles](#) page 235

encephalitis according to consensus criteria<sup>3</sup> were from papers that reported patient data individually. The authors extracted 50 lower-level psychiatric features reported in these 464 patients, defined their frequency, and grouped them into eight higher-level features. The psychopathological profile of each individual patient was then compared with 14 psychiatric comparator diagnoses using a principal component analysis and a constrained combination model. The authors also assessed whether individual patients were best described by one or by several psychiatric diagnoses.

The authors observed that patients had up to 20 lower-level psychiatric features (median three, IQR 2–5). More specifically, a transdiagnostic cluster of seven clinical features (agitation, aggression, hallucinations, delusions, mutism, irritability or mood instability, and depressed mood) explained 77% of the variance in the data. The most common higher-level features were behaviour (316 [68%]), psychosis (310 [67%]), mood (219 [47%]), catatonia (137 [30%]), and sleep disturbance (97 [21%]), and these features frequently coexisted in individual patients. Modelling these results showed that NMDAR-antibody encephalitis psychopathology is best described as a mixed mood-psychosis syndrome rather than by any single diagnosis alone. A network analysis confirmed the strong interconnection between psychiatric features within individual patients.

This study used advanced statistical analyses to provide an unprecedented depth and detail to NMDAR-antibody encephalitis psychopathology. Additionally, the results can guide clinical decision making about lumbar punctures for CSF antibody analysis in patients with suggestive psychiatric syndromes. This will most likely lead to more rapid diagnoses and thus better outcomes in patients with NMDAR-antibody encephalitis.

The clinical information of this study was derived from individual case reports, which might be biased to highlight unusual features. However, deviations in demographics, aetiology, or neurological profiles were absent in the investigated sample of 464 patients. Furthermore, in a subgroup analysis of patients reported by psychiatrists, the description of psychiatric symptoms was even more detailed, which led to a further increase of symptom overlap in patients and higher coherence of symptoms in the network analysis. The authors suggest that more input by psychiatrists might have accounted for 117 (26%) of 451 patients presenting with only

a single higher-level feature (eg, only behavioural abnormalities, or only psychosis).

An important next step is assessing the prognostic value of the identified criteria in an independent patient sample, and deriving positive and negative predictive values of the diagnostic features identified in this study to enable even better guidance of clinical decision making, ideally in multicentre studies. The psychiatric features could also be integrated with the profile of cognitive impairment,<sup>7</sup> functional MRI findings,<sup>8</sup> and serum or CSF biomarkers<sup>9,10</sup> to create scores that predict long-term outcome in patients with NMDAR-antibody encephalitis.<sup>11</sup>

As also noted by the authors, it will be interesting to extend the methods employed here to a paediatric population, since children constitute about one third of patients with NMDAR-antibody encephalitis but present with a different balance of symptoms—for example, more frequent movement disorders and less frequent memory impairments. Indeed, another recent meta-analysis indicates that agitation is more likely and psychosis is less likely in NMDAR encephalitis in children compared with adult patients.<sup>12</sup>

In summary, Al-Diwani and colleagues<sup>1</sup> identified a psychopathological pattern of NMDAR-antibody encephalitis that could transform the clinical approach to psychiatric patients with suspected autoimmune encephalitis. Future prospective studies should quantify the diagnostic power of the patterns of psychiatric features analysed here, to help identify patients who should undergo a lumbar puncture for CSF antibody testing. Finally, this study emphasises the importance of a close interaction between psychiatrists and neurologists to achieve the best possible outcomes for patients with this neuropsychiatric disorder.

#### Carsten Finke

Department of Neurology, Charité – Universitätsmedizin Berlin, Berlin 10115, Germany  
carsten.finke@charite.de

I declare no competing interests.

Copyright © The Author(s). Published by Elsevier Ltd. This is an Open Access article under the CC BY 4.0 license.

- 1 Dalmau J, Lancaster E, Martinez-Hernandez E, Rosenfeld MR, Balice-Gordon R. Clinical experience and laboratory investigations in patients with anti-NMDAR encephalitis. *Lancet Neurol* 2011; **10**: 63–74.
- 2 Irani SR, Bera K, Waters P, et al. N-methyl-D-aspartate antibody encephalitis: temporal progression of clinical and paraclinical observations in a predominantly non-paraneoplastic disorder of both sexes. *Brain* 2010; **133**: 1655–67.

- 3 Graus F, Titulaer MJ, Balu R, et al. A clinical approach to diagnosis of autoimmune encephalitis. *Lancet Neurol* 2016; **15**: 391–404.
- 4 Titulaer MJ, McCracken L, Gabilondo I, et al. Treatment and prognostic factors for long-term outcome in patients with anti-NMDA receptor encephalitis: an observational cohort study. *Lancet Neurol* 2013; **12**: 157–65.
- 5 Herken J, Prüss H. Red flags: clinical signs for identifying autoimmune encephalitis in psychiatric patients. *Front Psychiatry* 2017; **8**: 25.
- 6 Al-Diwani A, Handel A, Townsend L, et al. The psychopathology of anti-NMDA receptor encephalitis in adults: a systematic review and phenotypic analysis of individual patient data. *Lancet Psychiatry* 2019; published online Feb 11. [http://dx.doi.org/10.1016/S2215-0366\(19\)30001-X](http://dx.doi.org/10.1016/S2215-0366(19)30001-X).
- 7 Finke C, Kopp UA, Prüss H, Dalmau J, Wandinger K-P, Ploner CJ. Cognitive deficits following anti-NMDA receptor encephalitis. *J Neurol Neurosurg Psychiatry* 2012; **83**: 195–98.
- 8 Peer M, Prüss H, Ben-Dayan I, Paul F, Arzy S, Finke C. Functional connectivity of large-scale brain networks in patients with anti-NMDA receptor encephalitis: an observational study. *Lancet Psychiatry* 2017; **4**: 768–74.
- 9 Makuch M, Wilson R, Al-Diwani A, et al. N-methyl-D-aspartate receptor antibody production from germinal center reactions: therapeutic implications. *Ann Neurol* 2018; **83**: 553–61.
- 10 Leypoldt F, Höftberger R, Titulaer MJ, et al. Investigations on CXCL13 in anti-N-methyl-D-aspartate receptor encephalitis: a potential biomarker of treatment response. *JAMA Neurol* 2015; **72**: 180–86.
- 11 Balu R, McCracken L, Lancaster E, Graus F, Dalmau J, Titulaer MJ. A score that predicts 1-year functional status in patients with anti-NMDA receptor encephalitis. *Neurology* 2018; **92**: e244–52.
- 12 Sarkis RA, Coffey MJ, Cooper JJ, Hassan I, Lennox B. Anti-N-methyl-D-aspartate receptor encephalitis: a review of psychiatric phenotypes and management considerations: a report of the American Neuropsychiatric Association Committee on Research. *J Neuropsychiatry Clin Neurosci* 2018; published online Dec 18. DOI:10.1176/appi.neuropsych.18010005.

## Trauma and post-traumatic stress disorder: children should be seen and heard



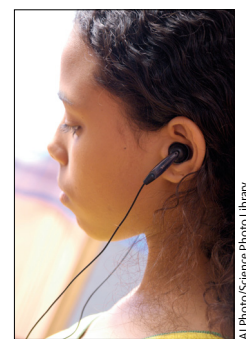
Experiencing trauma in childhood and adolescence—crucial periods for our developing brains and self-identity—has long been recognised as a risk factor for the development of psychopathology. In *The Lancet Psychiatry*, Stephanie Lewis and colleagues<sup>1</sup> present data from a twin-cohort study in England and Wales, the Environmental Risk study, with measures of trauma, psychopathology (including post-traumatic stress disorder [PTSD]), risk behaviours, and clinical service use. One of the many strengths of this study is the high rates of participation at follow-up. The research team should be lauded for their endeavour: this study is influential research that is of immediate value to clinicians and policy makers. Similar studies are now needed in other countries alongside validation of the risk calculator in independent cohorts.

A key finding from Lewis and colleagues' sample<sup>1</sup> is that almost a third of children were exposed to trauma, either directly or vicariously, within the range of internationally previously reported prevalence.<sup>2,3</sup> This finding indicates the need to determine the population level interventions capable of preventing trauma. Notably, and in keeping with the adult literature,<sup>4</sup> of traumatised children who go on to develop PTSD, the highest risk index trauma was of an interpersonal nature—ie, child maltreatment—reported in nearly half of the participants with PTSD. Clinicians and researchers must also establish whether interventions targeting risk factors<sup>1,3</sup> and resilience factors<sup>5</sup> for PTSD are beneficial, such that when a child is victimised the likelihood

of developing psychopathology can be reduced. Since the response of significant others, including family members, to a child's disclosure of trauma affects the child's subsequent risk of psychopathology,<sup>6</sup> a further target could be to increase social support and enable adults to respond to trauma disclosures in such a way that reduces stigmatisation, shame, and guilt. At a cognitive level, these interpersonal processes are thought to influence the manifestation of a constellation of negative beliefs about the self associated with shame, including, for example, "It was my fault", "I'm a bad person", and "I am defective". Together these negative self-schemata predict the subsequent development of more complicated psychopathology<sup>7</sup> and self-injury.<sup>8</sup>

As found in Lewis and colleagues' study,<sup>1</sup> trauma is not necessarily equivalent to PTSD. The trauma can be potentially associated with illnesses other than PTSD, capable of causing a trail of anguish in its wake. Trauma survivors had high rates of all measured adverse mental health outcomes, with odds ratios greatest for drug dependence (3.52, 95% CI 1.36–9.12) and psychotic symptoms (2.64, 1.38–5.04). Given the potentially complex nature of mental health problems experienced by childhood trauma survivors alongside poor prognosis and high readmission rates, this population would likely benefit from expert psychiatric trauma services.

From a global perspective, there is growing divergence between the ICD and DSM criteria for



See [Articles](#) page 247