a gambling disorder is confronted with EGMs. A more detailed understanding of the interactions between these machine design features and aspects of human decision-making and behaviours, including their interactions within vulnerable groups (adolescents, those with a mental illness, or under substantial psychosocial distress), will provide valuable insights for producing safer gambling products. The use of virtual reality and computational or decision neuroscience approaches can provide ecologically valid and real-time investigations of affective, cognitive, and physiological changes while gambling.

Urgent reform of EGM regulations to limit the impact of structural characteristics on gambling-related harm is needed. Opportunities abound for regulatory attention to reduce the prevalence and harm of gambling, including venue and machine accessibility, modification of EGM structural characteristics, enhanced user understanding and information, and use of systems to assist users to make and observe limits to gambling.[2] The time has come to prevent further damage associated with gambling and protect our communities.

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Pursuing functional connectivity in NMDAR1 autoantibody carriers

We read with interest the article by Michael Peer and colleagues.[1] The authors investigated by resting-state functional MRI (fMRI) a reasonable number of patients (n=43; 24 of which were reported previously) who were diagnosed earlier with so-called anti-NMDAR encephalitis (treatment regimens were not mentioned). It is acknowledged that a collection of patients with encephalitis who are also NMDAR1 autoantibody-positive is not easy to obtain. Of this collection, a large proportion had, on the day of fMRI, negative NMDAR1 autoantibody titres. In fact, only 17 of 43 patients were CSF positive and 27 of 43 were seropositive, if we consider a titre of 1:10 as a reasonable cut-off. Resting-state fMRI was done at highly variable timepoints after the initial diagnosis and led to the authors' conclusion of a "characteristic pattern of whole-brain functional connectivity alterations in anti-NMDAR encephalitis that is well suited to explain the major clinical symptoms of the disorder".

Undoubtedly, a sexy new method was applied to a hot topic. However, any conclusion linking the described connectivity disturbance to NMDAR1 autoantibodies is difficult based on these data which lack the adequate control. Only a well-matched control group of patients with encephalitis without history of NMDAR1 autoantibody positivity could allow any speculation in this direction. Healthy individuals are not a proper control. Although information on functional connectivity in age-matched and gender-matched healthy individuals provides some baseline for comparison, they do not allow dissecting the effects of NMDAR1 autoantibodies on brain connectivity. A proper control population would require the underlying inflammatory context of an encephalitic brain without NMDAR1 autoantibodies. A dysconnectivity syndrome can be expected in any kind of encephalitis.[2–4] In addition, the absence of NMDAR1 autoantibodies at the time of fMRI in a considerable number of individuals questions an ongoing influence of them on functional connectivity. Long-term persisting effects of NMDAR1 autoantibodies in their absence (ie, once they are eliminated by immunosuppression, plasmapheresis, or other means) have not yet been documented anywhere. They would also be difficult to prove non-experimentally. On a side note, catatonia is still classified as a positive symptom.

Future studies evaluating the importance of autoantibodies for brain functions should employ resting-state fMRI for standardised comparative assessment of different forms of acute and chronic encephalitides, including encephalitis with autoantibodies directed against brain epitopes, like NMDAR1 autoantibodies. In addition, NMDAR1 autoantibody carriers (all Ig classes)[5] with a compromised blood–brain barrier should be investigated using this method.

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Authors' reply

We thank Bárbara Oliveira and Hannelore Ehrenreich for their comments on our work.[1] Resting-state functional MRI (fMRI) is indeed a promising new imaging tool that already provided substantial insight into the pathophysiology of several neuropsychiatric disorders, including major depressive disorder, schizophrenia, and Alzheimer's disease.[2,3] Using resting-state fMRI, we identified a characteristic pattern of functional connectivity alterations in the largest cohort of anti-NMDA receptor encephalitis examined with MRI so far. These connectivity disturbances correlated with symptoms of psychosis and memory impairment and extend recent observations of hippocampal damage and white matter alterations.[4] Additionally, machine learning analyses based on resting-state fMRI data reliably distinguished patients from controls.

Notably, 86% of our patients were positive for IgG NMDAR antibodies at the time of imaging and all patients had CSF IgG NMDAR antibodies at diagnosis, the well-accepted hallmark of anti-NMDAR encephalitis. The significant resting-state fMRI connectivity disturbances, irrespective of antibody persistence or disease duration, indicate that the observed changes reflect long-term effects on brain activity. Long-term persisting deficits in meanwhile antibody-negative NMDAR encephalitis are rather the well-documented rule than the exception in the literature[5] and our clinical experience.

We respectfully disagree that healthy controls are not an adequate control group. A comparison with carefully matched healthy individuals is not only common practice in computational neuropsychiatry and functional neuroimaging, it is essential to identify disturbances of brain activity. Other autoimmune CNS disorders differ in their level of inflammation, the pathophysiological mechanisms, and affected brain regions, and therefore cannot provide a meaningful "inflammatory baseline". By contrast, preliminary analyses show that resting-state fMRI can distinguish characteristic connectivity alterations between anti-NMDAR encephalitis and other autoimmune encephalitides such as anti-LGI1 encephalitis. We therefore believe that resting-state fMRI can become a highly useful tool in the work-up of neuropsychiatric patients, potentially able to facilitate the differential diagnosis, treatment response, and follow-up. Indeed, this should include NMDAR antibody carriers of IgG, IgA, and IgM antibodies, given their association with cognitive impairments.[6]

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