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Antibody-mediated encephalitis and psychosis

The four cases of *N*-methyl-D-aspartate (NMDA) receptor antibody encephalitis with associated psychosis reported in December[1] raise an important and emerging issue and highlight that psychiatrists should include the condition in the differential diagnosis for patients presenting with acute psychosis. But there are some aspects that need clarification. The authors state that 'this case series demonstrates a new and treatable cause of psychosis', inferring that the association of psychosis with these antibodies was previously unknown. However, since the first 100 patients with NMDA receptor antibody encephalitis were reported in 2008,[2] this association has been well documented; psychosis is typically the first presentation and many cases were seen by psychiatrists before neurologists become involved.[2,3]

The association of these antibodies with psychosis is highly relevant because they bind to key neuronal surface proteins and are therefore likely to be pathogenic. Indeed, NMDA receptor antibody encephalitis is a condition that responds to immunotherapy and, importantly, there is thought to be an initial 'treatment window' for optimal immunomodulation.[4,5] The authors[1] speculate that 'there may be a pure psychiatric presentation associated with lower antibody titres'. Indeed, a recent study found that 3 out of 46 patients with first-episode psychosis (with no neurological or other clinically distinguishing features) had NMDA receptor antibodies.[6] One patient made a significant clinical improvement with plasmapheresis and steroid treatment. An additional patient had voltage-gated potassium channel antibodies, which can also be found in patients with other psychiatric presentations.[5,7] It now appears increasingly likely that other neuropsychiatric (e.g. catatonia) and psychiatric (e.g. obsessive–compulsive) symptoms may be associated with cell-surface neuronal antibodies.[8]

As Barry *et al*[1] point out, the condition does indeed provide some support for the NMDA receptor hypofunction hypothesis for psychosis. Some proponents of this theory have linked NMDA receptor hypofunction to first-rank psychotic symptoms in particular.[9] It is important that future studies of auto-antibody-associated psychosis characterise symptomatology in full, as this could allow for a level of clinical–pathological correlation rarely attained in psychiatry.

Declaration of interest

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1 Barry H, Hardiman O, Healy DG, Keogan M, Moroney J, Molnar PP, et al. Anti-NMDA receptor encephalitis: an important differential diagnosis in psychosis. *Br J Psychiatry* 2011; **199**: 508–9.

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6 Zandi MS, Irani SR, Lang B, Waters P, Jones PB, McKenna P, et al. Disease-relevant autoantibodies in first episode schizophrenia. *J Neurol* 2011; **258**: 686–8.

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Authors' reply: We thank Pollak *et al* for reiterating that anti-NMDA receptor encephalitis should be included as a differential diagnosis for patients presenting with acute psychosis. The association of anti-NMDA receptor encephalitis with psychosis is new, having been identified only as recently as 2008,[1] although the disorder has likely gone unrecognised and indeed untreated previously. Although to date there are no estimates regarding population prevalence rates of anti-NMDA receptor encephalitis, the California Encephalitis Project retrospectively screened 3000 patients with idiopathic encephalitis (with dyskinesia or movement disorders) and identified 10 (0.3%) anti-NMDA receptor-positive cases.[2] Examining the incidence of catatonia in psychosis, Fink & Taylor estimate a prevalence of between 9 and 17% of patients in academic psychiatry in-patient units,[3] while Peralta *et al* found that 31% of drug-naive patients with first-onset psychosis demonstrated at least one catatonic symptom, and found an interesting subgroup that showed a clear association with disorganisation and dyskinesia.[4]

The neuropsychiatric presentation underlying NMDA receptor encephalitis has only recently been published in the psychiatric literature.[5] Consequently, this clinical presentation involving psychiatric symptoms in approximately 77% of affected individuals has not been widely disseminated among psychiatrists. This was the driving force behind the publication of our case series.

Pollak *et al* restate our view that 'there may be a pure psychiatric presentation associated with lower antibody titres', and point to their own recent work showing that 3 out of 46 patients with first-episode psychosis had NMDA receptor antibodies.[6] This extremely important finding has profound

implications for future differential diagnoses of first-onset psychosis, potentially involving relevant auto-antibody and, specifically, anti-NMDA receptor screening. Further, plasmapheresis may be required and in some cases may even be clinically indicated before a diagnosis of NMDA receptor encephalitis is confirmed. This will have implications for hospital resources and will require close liaison between psychiatry and neurology services.

N-methyl-D-aspartate receptor hypofunction, whether due to exposure to phencyclidine ingestion, NMDA receptor auto-antibody or altered NMDA receptor trafficking,[7,8] is now implicated even more strongly in schizophrenia. Future studies focusing on this area may provide clues not only to the screening and management of NMDA receptor encephalitis among first-episode psychosis populations, but may also lead to a broader understanding of schizophrenia pathophysiology, with the potential for development of novel treatment strategies.

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Occipital transcranial magnetic stimulation in dementia with Lewy bodies

The results of Taylor *et al*'s study[1] are intriguing, shedding light on the pathogenesis of visual hallucinations in dementia with Lewy bodies.

However, I have some concerns about its methodology. The authors did not adopt the rather restrictive (and currently used) definition of phosphene threshold (i.e. the lowest stimulus intensity required to elicit phosphenes in 50% of trials), but used a much lower value (25%) to minimise the number of participants who might not respond. Moreover, to ensure inclusion of all individuals in analyses, participants who did not report phosphenes up to 100% stimulator output were arbitrated a phosphene threshold of 101%. The authors therefore assumed that not reporting phosphenes meant having a threshold above 100% because of an insufficient magnetic field strength from the stimulator to induce phosphenes in these individuals. However, as far as I know, to date there is no evidence definitely demonstrating such an assumption.

As a matter of fact, in most published studies of phosphene thresholds a certain number of participants do not experience phosphenes even with a maximum stimulator output. There are some reasons which may (partially) explain such a phenomenon.

First, it is possible that owing to methodological difficulties in mapping phosphene thresholds over each square millimetre of the occipital skull, the correct point for stimulation may not be identified in each participant.

Second, unlike primary motor cortex, primary visual cortex (calcarine fissure) is deeply located, lying in the mid-sagittal plane, so that the magnetic field strength applied over the entire skull may be insufficient to reach and stimulate the visual cortex. Regarding this aspect, it is noteworthy to consider that Taylor *et al* used a figure-of-eight coil (and not a circular one), which, although it is much more selective and has a higher spatial accuracy, stimulates a smaller cortical area,[2,3] and may generate, at least theoretically, a weaker electric current, resulting in a lower probability of evoking phosphenes.

Finally, as the authors stated, every millimetre the surface cortex is away from the stimulating coil, approximately an additional 3% of the maximum power output is required to induce an equivalent level of brain stimulation at the motor cortex (although no similar data on visual cortex stimulation are available in the literature). Such an aspect needs to be taken into account not only with regard to occipital cortical atrophy in affected patients compared with healthy controls, but also with regard to the fact that, because the lower portion of the visual cortex representing the upper visual field is farther from the scalp (as observed in magnetic resonance imaging), it is more difficult to elicit phosphenes with transcranial magnetic stimulation in the upper than in the lower visual field.[4] Although in the study an adjusted phosphene threshold ratio was performed to account for possible group differences in atrophy, it is not clear whether other aspects (anatomical differences in skull thickness and portion of visual cortex stimulated) were considered.

In the light of the above, I think that the authors should have performed a statistical analysis of phosphene threshold including only those participants in whom phosphenes were actually induced.

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Authors' reply: We agree that phosphene thresholds are typically defined at the 50% response rate level, although it should be recognised that the setting of a threshold is an arbitrary process. A number of our participants had thresholds near and