Reply

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In their Letter to the Editor, referring to our recent publication,[1] Lancaster and colleagues defend the construct of N-methyl-D-aspartate receptor (NMDAR) encephalitis. This defense is somewhat surprising, because we do not address this topic in our article.

We investigated seroprevalence of a broad range of autoantibodies (AB), directed against 24 different brain antigens, among them NMDAR1-AB, in a large number (N = 4,236) of healthy and neuropsychiatrically ill subjects. We found comparable presence of all of these AB in serum of both healthy and ill subjects, with respect to immunoglobulin (Ig) class and titer. Findings about Ig class in this work are presented both as total Ig as well as separately for IgG, IgA, and IgM. Even if all 1:10 titers were completely ignored in our data set (although scientifically solid evidence for such a cutoff is lacking), the overall titer distribution among healthy and ill subjects still remained similar.

In all our attempts so far to compare functionality of NMDAR1-AB of the various Ig classes in vitro and in vivo, we did not identify any fundamental differences (Hammer et al[2,3] and unpublished data), although they may well exist with respect to discrete biological effects at the cellular or systems level. We are not aware of any other publication that delivered a scientifically convincing back-to-back comparison of the various Ig classes of NMDAR1-AB regarding functionality.

Once again, we are not claiming in this article that NMDAR encephalitis does not occur, but we show that anti–NMDAR1-AB are not always pathogenic. Therefore, based on our data,[1] clinicians should be highly cautious with respect to any conclusions on a causal association of *serum* AB with brain disease. For more detailed information, the reader is kindly referred to our original publication.[1] As said earlier, the presence of these AB in the blood circulation does not allow any firm assumption as to whether they play a pathophysiological role in any brain-related syndromes, and certainly does not on its own justify immunosuppressive treatment, unless these AB are also proven to be present at substantial levels in the cerebrospinal fluid. AB of all types cross into the central nervous system at all times, for example, through the circumventricular organs (which lack a blood–brain barrier), and in the case of IgG are present in normal cerebrospinal fluid at about a 1:500 dilution of their blood concentration (IgA, 1:600; IgM, 1:3,000).[4]

Rather than trying to turn back the clock, we should learn more about these serum AB that are directed against brain antigens but not necessarily associated with any disease. These AB likely modify our brain functions if the blood–brain barrier becomes temporarily or persistently compromised.

Potential Conflicts of Interest

Nothing to report.

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References

1. Dahm L, Ott C, Steiner J, et al. Seroprevalence of autoantibodies against brain antigens in health and disease. Ann Neurol 2014;76:72–94.
2. Hammer C, Stepniak B, Schneider A, et al. Neuropsychiatric disease relevance of circulating anti-NMDA receptor autoantibodies depends on blood-brain barrier integrity. Mol Psychiatry 2014;19:1143–1149.
3. Hammer C, Zerche M, Schneider A, et al. Apolipoprotein E4 carrier status plus circulating anti-NMDAR1 autoantibodies: association with schizoaffective disorder. Mol Psychiatry 2014;19:1054–1056.
4. Reiber H, Peter JB. Cerebrospinal fluid analysis: disease-related data patterns and evaluation programs. J Neurol Sci 2001;184:101–122.

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Common Criteria for Electroencephalographic Evaluation in Patients with Disorders of Consciousness

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In their recent study, Forgacs et al highlighted the need for standard electroencephalographic (EEG) evaluation for characterizing patients with disorders of consciousness (DOC).[1] They analyzed EEG data with the aim of evaluating wakeful background organization and sleep architecture elements. They defined 4 categories of EEG organization based on a simple description of EEG features. Their results complemented previous data[2,3] obtained with the Synek scale.[4] The patterns classified as "normal" and "mildly abnormal" by Forgacs et al[1] would both be categorized as grade 1 on the Synek scale; they analyzed the data with the 2 patterns combined. Meanwhile, the patterns classified as "moderately abnormal" and "severely abnormal" are consistent with grades 2 and 3 of the Synek scale, respectively. However, in Forgacs et al's work,[1] background EEG refers mainly to frequency (and spatial distribution thereof); amplitude and reactivity were not assessed. In a recent study involving 106 patients, we found that each of the classical descriptors of standard EEG recordings (ie, amplitude, frequency, and reactivity) was related to the level of consciousness or 3-month outcomes.[5] Some EEG descriptors were specific to patients with unresponsive wakefulness syndrome (UWS) and others to patients in a minimally conscious state (MCS). Moreover, the cumulative amplitude–frequency–reactivity score allowed patients' outcomes to be better defined.[5]

Together, these works underscore the point that standard EEG has a clear diagnostic and prognostic relevance in DOC. Importantly, a normal or nearly normal EEG may contribute to differentiating locked-in syndrome from DOC with an ease not

obtainable through functional neuroimaging.[1] Despite the increasing consensus for inclusion of standard EEG in the neurophysiological evaluation of patients with DOC, several questions remain to be answered. In particular, it has not been clarified whether we should refer to common EEG patterns[1–3] or combine classic EEG descriptors.[5] Also, it has not been settled whether sleep architecture study adds significant information.[1] Moreover, it remains to be resolved whether a prolonged EEG recording is required to obtain essential data[1] or whether a standard-duration recording is adequate.[2,3,5] Data acquired from patients in a coma are scarcely useful because the pathophysiology of coma is different from that of UWS or MCS. Accordingly, it is our view that specific standardized criteria should be defined in the evaluation of EEG data obtained from these patients. Otherwise, neither patients nor clinicians will benefit fully from the advantages of EEG.

Potential Conflicts of Interest

Nothing to report.

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References

1. Forgacs PB, Conte MM, Fridman EA, et al. Preservation of electroencephalographic organization in patients with impaired consciousness and imaging-based evidence of command following. Ann Neurol 2014;76:869–879.
2. Bagnato S, Boccagni C, Prestandrea C, et al. Prognostic value of standard EEG in traumatic and non-traumatic disorders of consciousness following coma. Clin Neurophysiol 2010;121:274–280.
3. Boccagni C, Bagnato S, Sant'Angelo A, et al. Usefulness of standard EEG in predicting the outcome of patients with disorders of consciousness after anoxic coma. J Clin Neurophysiol 2011;28:489–492.
4. Synek VM. Prognostically important EEG coma patterns in diffuse anoxic and traumatic encephalopathies in adults. J Clin Neurophysiol 1988;5:161–174.
5. Bagnato S, Boccagni C, Sant'Angelo A, et al. EEG predictors of outcome in patients with disorders of consciousness admitted for intensive rehabilitation. Clin Neurophysiol (in press).

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A Proposed Role for Routine EEGs in Patients with Consciousness Disorders

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In their Letter to the Editor, Bagnato et al note the utility of standard electroencephalography (EEG) in diagnosis and prognostication of patients with disorders of consciousness (DOC) in early phases of recovery. These findings are consistent with our findings that chronic DOC patients with imaging-based evidence of covert command following demonstrate preservation of EEG organization as a canonical finding.[1] Thus, we agree that the use of EEG in assessments of DOC patients is likely to be useful, particularly in identifying immediate evidence of dissociation of motor behavior and large-scale network activity potentially supporting cognition.[1,2]

Because of the growing consensus, we would like to take this opportunity to propose that short EEG recordings should be included as standard in routine clinical evaluation and in design of research studies involving patients with DOC in addition to quantitative behavioral assessments (such as the Coma Recovery Scale–Revised[3]). The limitations are negligible, as standard EEG is cheap, widely available, and easily obtainable and has well-defined standards for interpretation.

This is important, as currently the accuracy of the clinical EEG categorization in separating behaviorally conscious from behaviorally unconscious patients is comparable[1] to highly sophisticated quantitative analysis of high-density EEG recordings performed only in a few highly specialized research laboratories.[4] Nevertheless, the question remains open whether a standard visual inspection of EEG recordings may actually be as useful in assessment of patients with DOC as more technically demanding analyses.

In addition, there are clear theoretical advantages of using long-term EEG recordings, including adequate sampling of wakeful and sleep stages: (1) significant fluctuations in clinical status are typical in this patient population, and the "best" behavioral state may be missed in a short recording; and (2) certain sleep features (ie, sleep spindles) are known markers of functional integrity of corticothalamic circuitry, which is also thought to be important in maintaining consciousness.[5] Additionally, presence of sleep spindles is clearly linked to prognosis of recovery after brain injury.[6] In our opinion, current efforts should further aim to include long-term EEG recordings in evaluation of patients who demonstrate evidence of preserved wakeful architecture if it is feasible.

However, large-scale multicenter studies will likely be needed to answer the questions about the utility of visual analysis of EEG in diagnosis and prognostication of patients with DOC.

Potential Conflicts of Interest

Nothing to report.

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References

1. Forgacs PB, Conte MM, Fridman EA, et al. Preservation of electroencephalographic organization in patients with impaired consciousness and imaging-based evidence of command following. Ann Neurol 2014;76:869–879.

2. Bardin JC, Fins JJ, Katz DI, et al. Dissociations between behavioural and functional magnetic resonance imaging-based evaluations of cognitive function after brain injury. Brain 2011;134:769–782.

3. Giacino JT, Kalmar K, Whyte J. The JFK Coma Recovery Scale-Revised: measurement characteristics and diagnostic utility. Arch Phys Med Rehabil 2004;85:2020–2029.

4. Sitt JD, King J-R, Karoui IE, et al. Large scale screening of neural signatures of consciousness in patients in a vegetative or minimally conscious state. Brain 2014;137:2258–2270.

5. Schiff ND. Recovery of consciousness after brain injury: a mesocircuit hypothesis. Trends Neurosci 2010;33:1–9.

6. Urakami Y. Relationship between sleep spindles and clinical recovery in patients with traumatic brain injury: a simultaneous EEG and MEG study. Clin EEG Neurosci 2012;43:39–47.

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