Prevalence of *N*-Methyl-Aspartate Receptor Autoantibodies in the Peripheral Blood: Healthy Control Samples Revisited

In March 2013, we published a study in *JAMA Psychiatry* assessing the prevalence of anti-\(N\)-methyl-D-aspartate glutamate receptor (NMDAR) serum autoantibodies in unmedicated acutely ill patients with schizophrenia, major depression (MD), borderline personality disorder (BLPD), and healthy control individuals without neuropsychiatric disorder.\(^1\) The laboratory analyses of this set of samples were done in 2010. \(N\)-methyl-D-aspartate glutamate receptor antibodies were identified in 15 patients, primarily in those with a clinical diagnosis of schizophrenia (12 of 121, 9.9%) as opposed to those with MD (2 of 70, 2.9%), those with BLPD (0 of 38, 0%), and control individuals (1 of 230, 0.4%). Two patients were initially misdiagnosed as having catatonic or disorganized schizophrenia. Retrospectively, these cases were reclassified as cases with NMDAR encephalitis (presence of specific IgG anti-NR1a autoantibodies in both serum and cerebrospinal fluid).

Methods | Driven by a recent publication of Hammer et al\(^2\) showing a higher seroprevalence of anti-NMDAR autoantibodies in healthy control individuals compared with our publication (137 of 1272, 10.8% vs 1 of 230, 0.4%), we set out to assess whether this finding might be reproducible in our local center. Accordingly, we reanalyzed all currently available blood samples from acutely ill unmedicated psychiatric patients and matched control individuals from the scientific biobank at the University of Magdeburg’s Department of Psychiatry (Table, eTable in Supplement).\(^1\) The sample collection was approved by the University of Magdeburg ethics committee and written informed consent was obtained from patients.\(^3\) Current commercial indirect immunofluorescence BIOCHIP assays (Neurology-Mosaic-6 and Neurology-Validation-Mosaic) were applied at the reference laboratory of EUROIMMUN.

Results | The Table summarizes the results from cell-based assays (CBAs) with fixed NR1a-expressing cells. The percentage of blood samples with IgA, IgG, or IgM NR1a anti-NMDAR autoantibodies again tended to be higher in patients with schizophrenia (18 of 184, 9.9%) compared with those with MD (5 of 99, 5.1%), those with BLPD (1 of 42, 2.4%), and healthy control individuals (25 of 357, 7.0%). However, the diagnostic group difference were not statistically significant (\(\chi^2_{3,682} = 0.260\)). This finding was mainly attributable to the detection of a higher seroprevalence of NMDAR antibodies in healthy control participants than in our previous publication.\(^1\) The results from respective CBAs with fixed NR2a- or NR2b-expressing cells were negative in all tested samples.

Random sampling effects might have contributed to the different results in previously (2010) and recently (2013) tested healthy control samples. However, even if the prevalence of anti-NMDAR autoantibodies was higher in the non-overlapping vs overlapping control cohort (8.7% vs 4.0%,

### Table. Prevalence of Anti-NMDAR NR1a Antibodies in the Peripheral Blood of Patients and Control Individuals

<table>
<thead>
<tr>
<th>Study Group</th>
<th>Anti-NMDAR NR1a Positivity, No. (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Any</td>
</tr>
<tr>
<td>Control (all participants, n = 357)</td>
<td>25 (7.0)</td>
</tr>
<tr>
<td>OL (n = 126)</td>
<td>5 (4.0)</td>
</tr>
<tr>
<td>No OL (n = 231)</td>
<td>20 (8.7)</td>
</tr>
<tr>
<td>Schizophrenia (all participants, n = 184)</td>
<td>18 (9.8)</td>
</tr>
<tr>
<td>OL (n = 117)</td>
<td>10 (8.5)</td>
</tr>
<tr>
<td>No OL (n = 67)</td>
<td>8 (11.9)</td>
</tr>
<tr>
<td>Major depression (all participants, n = 99)</td>
<td>5 (5.1)</td>
</tr>
<tr>
<td>OL (n = 70)</td>
<td>1 (1.4)</td>
</tr>
<tr>
<td>No OL (n = 29)</td>
<td>4 (13.8)</td>
</tr>
<tr>
<td>Borderline personality disorder (all participants, n = 42)</td>
<td>1 (2.4)</td>
</tr>
<tr>
<td>OL (n = 35)</td>
<td>1 (2.9)</td>
</tr>
<tr>
<td>No OL (n = 7)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>Total (N = 682)</td>
<td>49 (7.2)</td>
</tr>
</tbody>
</table>

Abbreviations: NMDAR, \(N\)-methyl-D-aspartate glutamate receptor; OL, overlap (overlap of individuals with our previously published study).\(^1\)
patients with NMDAR encephalitis suggest that cerebrospinal fluid anti-NMDAR autoantibody titers show a much better correlation with clinical symptoms than blood autoantibody titers.3,4,6

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