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Review

# EEG findings in NMDA encephalitis – A systematic review

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ABSTRACT

*Purpose:* The clinical utility of EEG in cases of NMDA encephalitis is broad with many findings indicating not just epileptiform activity but also encephalopathy and potentially providing insights into pathophysiologic mechanisms of disease. We aimed to determine the frequency of different abnormalities described on EEG and their association with outcome in patients affected by NMDARE through a systematic review of all cases published.
*Method:* A systematic literature review of PubMed and Embase of all published cases of anti-NMDA receptor encephalitis with EEG results, was performed from inception to January 2018.
*Results:* A total of 446 cases of anti-NMDA receptor encephalitis with reported EEG findings were identified. 373 EEGs were abnormal, and this strongly correlated with ICU admission and time to recovery ($p = 0.014$ and 0.04 respectively). ICU admission and recovery were also correlated with delta range abnormalities including extreme delta brush ($p = 0.007$ and 0.03). Electrographic seizures correlated strongly with clinical seizures ($p < 0.0001$), however only 39 cases had EEG seizures captured, while there were 294 cases with clinical seizures.
*Conclusions:* EEG is useful in the clinical management and prognostication of cases on NMDA encephalitis. This is particularly true of certain findings which portend a higher likelihood of ICU admission or poorer outcome and this may assist in the decision to pursue more aggressive treatment options.

## 1. Introduction

*N*-methyl-D-aspartate receptor encephalitis (NMDARE) is becoming a well-recognised cause of symptomatic seizures in the context of an encephalitic illness. Directly pathogenic anti-NMDA receptor antibodies bind to the glutamate subunit of the NMDA receptor, leading to receptor capping and internalisation [1–3]. Neuronal dysfunction in fronto-striatal connections and prefrontal networks, leads to the clinical symptom clusters including psychiatric features, movement disorders, autonomic disturbances and seizures. This is thought to be due at least in part to the over-representation of NMDA receptor subunit NR2B in the prefrontal cortex, which is critical in processing working memory, emotions and consciousness [4]. Clinical seizures are common, occurring in 70–80% of cases, but are rarely seen at first presentation in adults [1,2,5,6].

The electroencephalogram (EEG) is almost always (90–100%) abnormal in cases of NMDARE and typically shows generalised or predominantly frontotemporal slowing [1,5–7]. Epileptogenic abnormalities are less common, seen in 24–50% of cases, and are possibly more common during the early stage of the illness [7]. The "extreme delta brush" (EDB) pattern (a nearly continuous combination of symmetric and synchronous frontally predominant delta activity with overriding fast activity has been suggested to be specific for NMDARE, and has been associated with poor prognosis and prolonged hospitalisation [8].

Early diagnosis is important because prompt treatment is associated with improved outcome [2,6]. Behavioural disturbance and psychiatric symptoms are the most common features at presentation (67–77%) [7,9]. EEG is potentially useful to discriminate between organic and psychiatric pathology, whereas MR brain imaging is often unhelpful [2,6,10]. Definite diagnosis requires demonstration of NMDAR antibodies in CSF, and testing may take substantial time to be completed. EEG might also have potential as a biomarker of disease severity to guide treatment decisions while awaiting CSF results.

Therefore, our primary aim was to determine the frequency of different abnormalities described on EEG in patients affected by NMDARE

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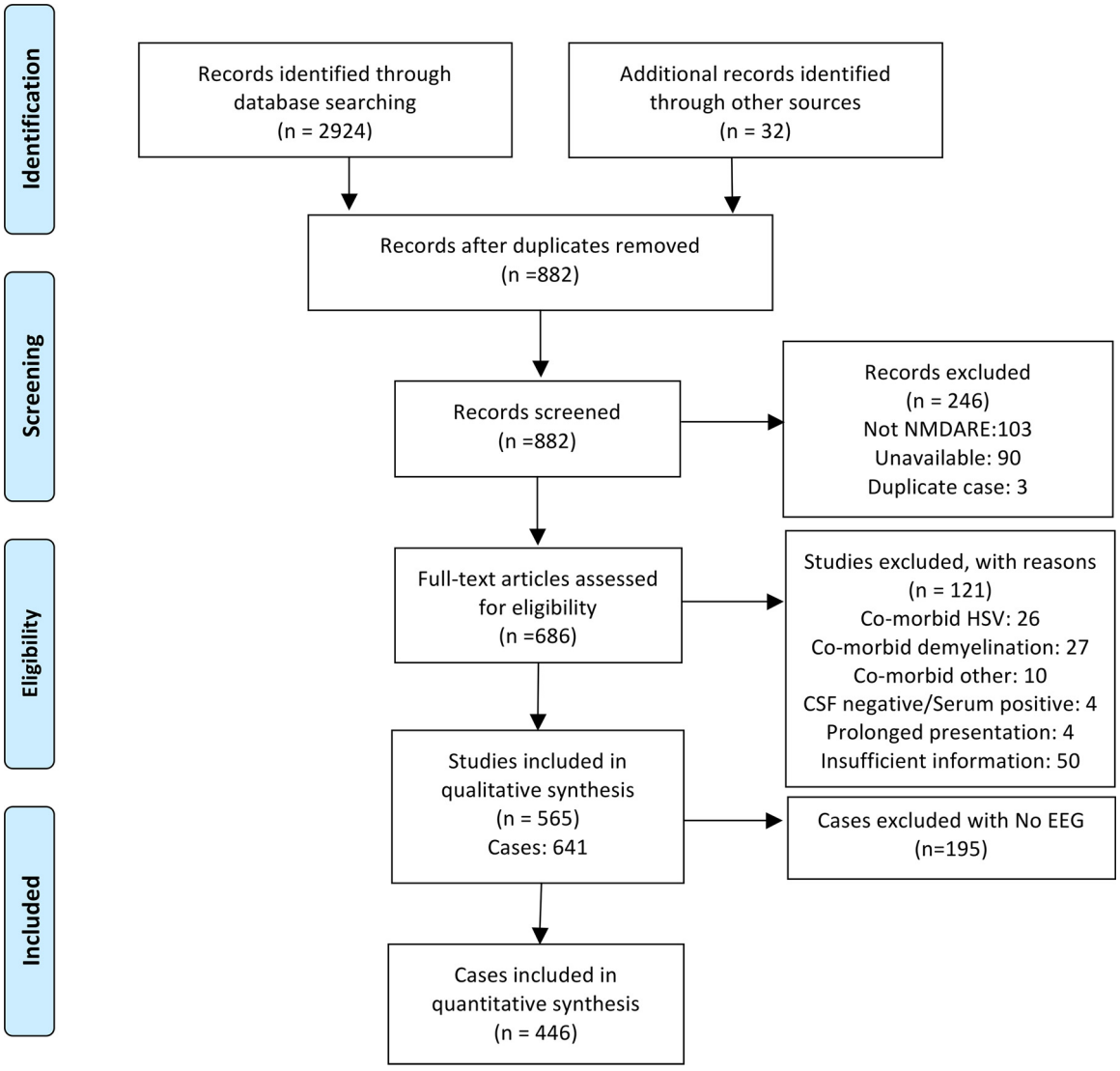


**Fig. 1.** PRISMA 2009 flow diagram: published cases of anti-NMDA receptor encephalitis. From: [11] For more information, visit www.prisma-statement.org.

through a systematic review of all cases published. We also aimed to determine if any of these features might be associated with disease progression or outcomes and therefore be useful in prognostication.

## 2. Methods

PubMed and Embase (Inception to January 2018) were first searched to identify all cases of anti-NMDA receptor encephalitis, using search terms: NMDA, NMDAR, NMDARE, N-methyl-D-aspartate encephalitis. Results were restricted to case reports and series, including conference and poster abstracts. Two authors (NW, CO) independently performed search and screening of abstracts. References of selected articles were also reviewed to identify other eligible studies. The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement recommendations were followed (see Fig. 1) [11].

Cases were included if there was appropriate clinical symptoms and adequate details of EEG findings, with documentation of positive IgG serum and/or CSF anti-NMDA receptor antibody. Suspected cases without antibody confirmation in serum or CSF were excluded. Cases which had NMDA antibody excluded by a negative CSF result (4) or > 12 months delay from first to second symptom clusters (4) were also excluded given the lack of diagnostic clarity. Additionally, cases with significant active co-morbid diagnoses that could complicate the clinical picture were excluded, for example: herpes simplex virus (HSV) encephalitis (26), Japanese encephalitis (4), neurosyphilis (2), demyelinating disorders (27), neurological malignancy (2) and malignancy with active chemotherapy (2). When there was disputed eligibility for inclusion, the case was discussed with all authors and consensus reached. (Excluded cases are described in Table 1).

Data collected included demographics, initial and subsequent clinical presentation of encephalitis, timing of symptoms, investigations, treatments and outcomes. EEG findings were categorised according to clinically relevant features. Background slow, diffuse and generalised slowing were all considered markers of encephalopathy. Delta range slowing and EDB were considered markers of severe encephalopathy. Sharp waves, periodic lateralised discharges or generalised periodic discharges were categorised as epileptiform discharges. Electrographic seizure or status epilepticus were categorised as ictal events. Missing data were noted.

### 2.1. Statistical analysis

Continuous variables were summarised with mean and standard deviations and categorical variables with counts and percentages. Associations between categorical variables were assessed with cross-classification tables and analysed using likelihood ratio chi-squared

**Table 1**
Excluded cases of Anti-NMDA receptor encephalitis.

| **N** | | **74** |
|---|---|---|
| Female gender | | 43 (58.1%) |
| Mean age | | 28.7 years (SD 20.5) |
| **CSF negative/Serum positive** | | **4** |
| **Prolonged presentation/Inaccurate reporting** | | **4** |
| **Co-existent / co-morbid condition** | | **66** |
| Demyelination (ADEM, NMO, MS) | | 27 |
| Herpes zoster encephalitis (CSF positive) | | 26 |
| Other | | 13 |
| - Infections | Japanese encephalitis | 4 |
| | Neurosyphilis | 2 |
| | HIV encephalitis | 1 |
| | Angiostrongylus cantonensis | 1 |
| - Malignancy | Glioblastoma | 1 |
| | Hodgkin's lymphoma (nodular sclerosing) | 1 |
| | Non-small cell lung cancer and stroke | 1 |
| | Metastatic melanoma, cerebral metastases | 1 |
| - Unknown | Generalised dystonia for 9 years prior | 1 |
| **EEG not performed** | | **195** |

tests. For 2 × 2 tables odds-ratios with 95% confidence intervals were also presented. Time to recovery was analysed using Kaplan-Meier curves with log-rank tests.

## 3. Results

There were 882 articles found in initial search and screening and 317 articles were excluded for reasons outlined in Fig. 1. Of those remaining, 565 articles with 641 cases were reviewed and 446 cases containing EEG data were included in the analysis. There were 343 (76.9%) female and 103 (23.1%) male cases with mean age 22.2 (SD 15.1) years (range 8 months – 84 years). The most common presenting symptom was behavioural disturbance (224 cases, 51.0%). Mean time to diagnosis was 17.6 days. Cerebrospinal fluid analysis was performed in 349 cases and was abnormal in 270 (77.3%). Abnormalities included lymphocytic pleocytosis (242, 54.1%), elevated protein (91, 20.4%) and presence of oligoclonal bands (60, 13.4%). All included cases that underwent CSF analysis had NMDA antibody detected in CSF. MRI was performed in 404 cases and was abnormal in 132 (32.6%) cases.

EEG findings are outlined in Table 2. EEG was abnormal in 373 (83.6%) cases, most commonly with changes of diffuse encephalopathy (269 cases). Delta range abnormalities were reported in 101 cases, including 20 cases with generalised rhythmic delta activity (GRDA) and 30 cases with EDB. Diffuse beta activity was seen in 13 cases.

**Table 2**
EEG findings in Anti-NMDA receptor encephalitis.

| *EEG finding* | *N* | *% of abnormal EEGs* | *% of total cases* |
|---|---|---|---|
| **Encephalopathy** | **269** | **72.11%** | **60.31%** |
| Delta range slowing | 81 | 21.71% | 18.16% |
| Extreme delta brush (EDB) | 30 | 8.04% | 6.72% |
| Generalised rhythmic delta activity (GRDA) | 20 | 5.36% | 4.48% |
| Diffuse beta activity | 13 | 3.48% | 2.91% |
| Focal abnormality | 82 | 21.98% | 18.38% |
| Epileptiform abnormality | 67 | 17.96% | 15.02% |
| Sharp waves | 48 | 12.87% | 10.76% |
| PLEDs | 13 | 3.48% | 2.91% |
| GPEDs | 6 | 1.61% | 1.34% |
| Lateralisation to left hemisphere | 42 | 11.26% | 9.42% |
| Lateralisation to right hemisphere | 36 | 9.65% | 8.07% |
| Bilateral changes | 10 | 2.68% | 2.24% |
| Seizures | 39 | 10.45% | 8.74% |
| Status epilepticus | 13 | 3.48% | 2.91% |

**Table 3**
EEG findings in Anti-NMDA receptor encephalitis.

| *EEG finding* | *N* |
|---|---|
| No focal abnormalities | 290 |
| Central | 2 |
| Centro-parietal | 1 |
| Frontal | 10 |
| Frontal and occipital | 1 |
| Frontal and temporal | 1 |
| Frontocentral | 1 |
| Frontotemporal | 14 |
| Frontotemporal and central | 1 |
| Frontotemporal and parietal | 1 |
| Occipital | 3 |
| Parietal | 3 |
| Parieto-occipital | 2 |
| Posterior | 1 |
| Temporal | 36 |
| Temporal and occipital | 2 |
| Temporal and parietal | 1 |
| Temporo-occipital | 2 |

Encephalopathic changes on EEG was significantly correlated with a clinical presentation of behavioural disturbance ($p = 0.03$). There was no other correlation between EEG abnormality and clinical presentation. EDB was not associated with the presence of oro-facial dyskinesia or movement disorder, suggesting that EMG artefact is not responsible for this pattern. There was a significant negative association between EDB and seizures ($P = 0.0002$).

Focal abnormalities (slowing or epileptiform discharges) were reported in 82 cases (18.4%), most commonly in temporal (36 cases), frontotemporal (14 cases) and frontal (10 cases) regions, see Table 3. These abnormalities were more commonly lateralised to the left (51.8%) than right (44.4%) hemispheres (not reported in the remainder). Focal abnormalities on EEG were significantly correlated with presence of focal abnormalities on MR imaging ($p = 0.007$). Epileptiform discharges were seen in 67 cases (15.0%), most commonly regional sharp waves (48 cases), periodic lateralised epileptiform discharges (PLEDs) (13 cases), or generalised periodic epileptiform discharges (GPEDs) (6 cases).

Seizures were the first presenting symptom in 84 (18.8%) cases and occurred at some point during the illness in 294 (65.9%) cases. However, epileptiform discharges were seen in 67 cases, and electrographic seizures in only 39 cases including 13 individuals with status epilepticus. There was no correlation between presence of electrographic seizures or epileptiform discharges on EEG and ICU admission or poor outcome. Electrographic seizures correlated strongly with clinical seizures ($p < 0.0001$).

A total of 150 cases (33.6%) required ICU admission. An abnormal EEG correlated strongly with requirement for ICU admission (OR = 2.04 (95% CI 1.13, 3.69), $p = 0.014$). The presence of delta range abnormalities including EDB were also strongly correlated with ICU admission (OR = 1.92 (95% CI 1.20, 3.07), $p = 0.007$).

Average time to recovery was 162.9 days in cases with normal EEG and 242.5 days in cases with EEG abnormalities. Presence of delta range abnormalities including EDB, were significantly associated with incomplete recovery (OR = 2.23, (95% CI 1.09, 4.56), $p = 0.03$). There was a trend towards significance for the correlation between normal EEG and full recovery ($p = 0.058$). This became significant when accounting for age and gender (OR 1.77 95% CI (1.01, 3.12), $p = 0.046$). There was no significant association between type of symptom at presentation and outcome. Recovery was not reported in 65 cases.

There was no significant difference between cases identified that did not undergo EEG testing with respect to age or gender ($p = 0.14$, 0.86 respectively). There was also no difference in total recovery, time to recovery or requirement for ICU admission ($p = 0.79$, 0.81, 0.08 respectively).

## 4. Discussion

We found that non-specific EEG changes consistent with encephalopathy were the most frequent abnormalities seen in NMDARE. An abnormal EEG was associated with increased likelihood of admission to ICU and incomplete recovery, suggesting that EEG should be performed in all cases of suspected NMDARE. It is notable that almost 30% of cases identified in initial screening did not have EEG findings reported. Severe generalised slowing (delta range frequencies), or presence of EDB, further increased the likelihood for ICU admission and incomplete recovery and these findings could be considered poor prognostic indicators which supports the findings of prior studies [8,12]. Importantly abnormalities of MRI were only seen in 32.6%, so EEG is potentially more useful, especially as CSF analysis can be prolonged [6].

EEG is commonly used to differentiate between primary psychiatric disorders and organic disease. The rate of abnormal EEG in the NMDARE population (83.6% in this study) is higher than the rate of abnormal EEG in psychiatric patients undergoing "screening" EEG (17–19%) [13,14]. Antipsychotic medications may increase the rate of EEG abnormalities (up to 74% in patients treated with clozapine), limiting the value of EEG in this population [15,16]. Maintaining a high level of suspicion for NMDARE and testing CSF when clinically indicated by the development of seizures, movement disorder or autonomic dysfunction is recommended [9].

Despite a high proportion of cases experiencing clinical seizures (65.9%), electrographic seizures and sharp waves were uncommon. This may reflect timing of EEG during a long illness, or a highly localised and/or deep location of the epileptogenic zone, such as the perisylvian or mesial prefrontal regions. Long-term monitoring of NMDARE patients has shown abnormal seizure-like movements in the absence of EEG abnormalities suggesting dyskinesia may mimic seizure [5]. If EEG is unavailable, seizures should be treated presumptively to avoid undertreatment of status epilepticus. Available data were insufficient to analyse abnormal movements or semiology of seizures in these cases. Further research is needed to clarify if these seizure-like movements are epileptic in origin, and detailed descriptions of semiology could guide insights into specific network involvement and the underlying pathogenesis of antibody mediated epileptogenesis.

The EDB pattern has been an attractive concept for EEG research in NMDARE but was infrequently seen in these cases (30 out of 373). This may be due to timing of EEGs performed, since EDB seems to appear at the peak of disease severity [17]. EDB may not be specific for NMDARE but instead be a marker for severe encephalopathy and this is supported by the findings that delta range slowing (but without brushes) has a similar association with outcome [18]. EDB is thought to arise from disruption of glutamatergic neurotransmission, resulting in deafferentation and slow thalamocortical oscillations [19]. This is supported by Ketamine EEG models and Schizophrenia models [20,21]. In general, cerebral network stability depends on proportionality of inhibitory and excitatory post synaptic potential frequencies and the time decay constant. In particular, the function of NMDA is crucial for network rate control (by slow gating kinetics) and to sustain partially synchronised network dynamics produced by faster frequencies [22]. Failure of network stabilisation in NMDARE may cause an imbalance of fast and slow activity and may explain why beta and delta range abnormalities are a more common finding in severe disease. The present data is also in line with previous work which suggests that this pattern is not epileptogenic, and the presence of physiologic beta frequencies cannot be considered synonymous with epileptic fast activity [23,24].

Focal abnormalities on EEG were infrequent (seen in 18.4%) and distributed throughout the brain. The most common regions with abnormalities were the temporal and frontotemporal regions. Focality may reflect regional variations in receptor density or susceptibility to antibody binding. In NMDARE, seizure semiology and recorded ictal onset on surface EEG has been reported in both temporal and extratemporal locations [25,26]. In particular, the perisylvian region and specifically the insula, have also been implicated [27–29]. Even when EEG abnormalities are located in the temporal region, the epileptic zone may lie outside the temporal lobe due to dense interconnections between mesial temporal lobe, perisylvian and limbic networks. For example, EEG abnormalities in the insula-opercula region may manifest in mid-temporal regions [30]. Clarification of this would inform our understanding of the regional preferences of NMDA antibodies and potentially the mechanisms underlying the genesis of clinical manifestations.

Another area which remains unclear is the mechanisms of seizure generation and epileptogenesis. The relationship between NMDAR and epilepsy is complex and poorly understood. The effects of NMDAR internalisation or capping may be extrapolated from the known effects of ketamine (a non-competitive NMDA receptor antagonist). Ketamine has a complex effect on epileptogenicity. At low doses, ketamine may provoke or prolong seizures. While at higher doses, ketamine induces sedation and can reduce or eliminate seizure activity and has been used to treat refractory status epilepticus [31,32]. In animal models, low dose ketamine increased release of excitatory neurotransmitters (glutamate, dopamine and acetylcholine), and higher doses reduced glutamate levels [33,34]. This may at least in part explain why seizure generation has not occurred in animal models of NMDARE, and why seizures are typically seen in the early phases of illness [2,35]. The predominance of NMDAR mediated effects in the developing brain might also explain why seizures are more commonly the first presenting symptom in the paediatric population [5].

The nature of this study brings a number of methodological limitations. Reporting and publication bias are relevant. Selection bias may also be contributory as indication for EEG was rarely reported and may have been prompted by particular clinical features or severity. Relevant clinical data, such as seizure semiology, timing of the EEG, and the complete EEG recordings were unavailable for examination. Lack of standardisation of EEG terms and variable expertise of reporting doctor also limit the conclusions that may be drawn from this analysis. It is important to note that available recovery data were limited, since most cases were not followed up for a sufficient time ($< 2$ years) to confirm that recovery was incomplete.

## 5. Conclusion

EEG is useful in the clinical management and prognostication of cases on NMDA encephalitis. This is particularly true of delta range abnormalities and EDB which portend a higher likelihood of ICU admission or poorer outcome and this may assist in the decision to pursue more aggressive treatment options. While clinical seizures are common, electrographic evidence of epileptic activity is uncommon which potentially reflects a deeply located or highly localised epileptogenic zone. Further work is needed to understand the epileptogenesis of seizures in NMDARE.

## Ethical statement

We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

## Disclosure

None of the authors report any disclosures.

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