



# Structural brain changes and clinical outcomes of patients with NMDA receptor encephalitis in Germany: a cross-sectional study



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## Summary

**Background** Many patients with N-methyl-D-aspartate receptor (NMDAR) encephalitis show persistent neurological or psychiatric symptoms, despite immunotherapy. The neuroanatomical basis of these symptoms remains uncertain. Morphological complexity analysis with fractal dimensionality has emerged as a sensitive neuroimaging method in related conditions, but remains unexplored in autoimmune encephalitis. We aimed to characterise morphological brain complexity, symptom trajectories from peak illness to the post-acute stage, and the relationship between structural brain changes and post-acute outcomes in patients with NMDAR encephalitis.

**Methods** In this cross-sectional study, we included patients with post-acute NMDAR encephalitis referred to Charité–Universitätsmedizin Berlin, Germany. Patients were matched (1:1) to healthy control participants for sex and age by use of logistic regression propensity scores and nearest-neighbour matching. Data were collected between July 18, 2011, and March 17, 2021. Patient outcomes were assessed with the modified Rankin Scale (mRS), Clinical Assessment Scale for Autoimmune Encephalitis (CASE), psychiatric phenotyping, and neuropsychological testing. Morphological brain complexity was quantified from T1-weighted structural MRI. Normative modelling was used to evaluate the relationship between structural brain changes and post-acute outcomes. Self-reports on post-acute symptoms by individuals with lived experience informed the study design.

**Findings** We included 70 patients (60 [86%] female and ten [14%] male; mean age 28·1 years [SD 10·2; range 15·0–67·0]) and 70 age-matched and sex-matched healthy control participants (60 [86%] female and ten [14%] male; 29·0 [9·3; 16·0–65·2]; ethnicity data unavailable). Study visits occurred at a median of 22·2 months from disease onset (IQR 8·5–42·5). Patients were severely affected at peak illness, but showed significant clinical improvement in both mRS (median 5 vs 1,  $Z = -7·2$ ,  $p < 0·0001$ ) and CASE (median 11 vs 1,  $Z = -7·2$ ,  $p < 0·0001$ ) in the post-acute stage. Nevertheless, 47 (67%) patients continued to show residual CASE symptoms, most commonly memory dysfunction (43 [61%]) and psychiatric symptoms (25 [36%]). In patients with persistent symptoms, psychiatric manifestations shifted from a psychosis-dominant phenotype at peak illness to an affective-dominant phenotype in the post-acute stage. Brain imaging showed a characteristic pattern of reduced morphological complexity, including the hippocampus bilaterally and a fronto-cingulo-temporal cluster in grey and white matter. Normative modelling revealed that patients with persistent symptoms showed stronger alterations of brain morphology than those without (psychiatric symptoms:  $t = -2·65$ ,  $p = 0·0100$ ; memory dysfunction:  $t = -3·98$ ,  $p = 0·0002$ ; both vs no symptoms  $t = -5·46$ ,  $p < 0·0001$ ). Similarly, stronger morphological alterations were associated with lower visuospatial and verbal memory performance (all  $p_{FDR} < 0·015$ ).

**Interpretation** Post-acute NMDAR encephalitis is characterised by systematic alterations of brain morphology. These changes are associated with persistent psychiatric symptoms and memory dysfunction after immunotherapy, highlighting fractal dimensionality as a promising new imaging marker of long-term outcomes. The phenotypic shift in psychiatric symptoms and the persistence of memory dysfunction highlight the importance of structured post-acute care to address long-term affective and cognitive morbidity in patients with NMDAR encephalitis.

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## Introduction

N-methyl-D-aspartate receptor (NMDAR) encephalitis represents the most common form of autoimmune encephalitis.<sup>1</sup> First discovered in 2007, NMDAR encephalitis is caused by autoantibodies against the

GluN1 subunit of the NMDA receptor, which plays a key role in glutamatergic signalling, long-term potentiation, and synaptic plasticity across the brain.<sup>1</sup> Clinically, NMDAR encephalitis causes a severe acute syndrome including cognitive dysfunction, psychiatric symptoms,

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## Research in context

### Evidence before this study

Since its discovery in 2007, N-methyl-D-aspartate receptor (NMDAR) encephalitis has been recognised as the most common form of autoimmune encephalitis. Although most patients improve with immunotherapy in terms of global functional outcome, long-term recovery can be protracted, and many patients experience substantial residual symptoms for years after disease onset. Importantly, self-reports by people with lived experience have identified this post-acute symptom burden as a major barrier to convalescence and social reintegration. However, the neuroanatomical basis of this long-term morbidity remains poorly understood. We searched PubMed and Google Scholar, without language restrictions, from database inception to Sept 21, 2025, using the terms: “anti-NMDA receptor encephalitis”, “anti-N-methyl-D-aspartate receptor encephalitis”, “NMDAR”, “NMDA receptor”, “NMDA antibody”, and “autoimmune encephalitis”. Previous neuroimaging studies have identified the hippocampus as a major disease target, but findings on cortical changes and white matter alterations are less consistent, and their relationship to post-acute outcomes remains unclear. Fractal dimensionality analysis represents a sensitive new morphometric approach for detecting subtle alterations of brain structure from anatomical MRI data. Despite promising results in both psychiatric and neuro-immunological conditions, the framework has not yet been applied to autoimmune encephalitis.

### Added value of this study

Using one of the largest neuroimaging datasets to date, our study identifies an association between structural brain changes and clinical outcomes of patients with NMDAR encephalitis. Clinically, around two-thirds of patients showed persistent symptoms despite immunotherapy, with memory dysfunction and psychiatric symptoms representing the most prevalent domains. By analysing symptom evolution over time, we identify a phenotypic shift in the psychiatric manifestations of NMDAR encephalitis, marked by a transition from a psychosis-dominant phenotype at peak illness to an affective-dominant phenotype in patients with persistent psychiatric morbidity in the post-acute stage. Furthermore, patients with persistent

psychiatric symptoms (around a third) showed different rates of acute symptoms than patients whose psychiatric symptoms resolved after peak illness (about two-thirds), calling for future studies to investigate if acute psychopathological symptom clusters could be used to identify patients at risk for later psychiatric morbidity. Fractal dimensionality analysis of anatomical MRI revealed a characteristic pattern of structural brain changes, involving the hippocampus and a fronto-cingulo-temporal cluster in grey and white matter. Using normative modelling, we show that these brain changes are more pronounced in patients with persistent symptoms than in those without, highlighting fractal dimensionality as a promising new imaging marker of long-term outcomes. Notably, fractal dimensionality does not require specialised MRI sequences but can be estimated from T1-weighted images, facilitating its use in future research and potentially clinical applications.

### Implications of all the available evidence

Together with exiting evidence, our findings support the view that long-term recovery from NMDAR encephalitis is frequently incomplete. Although acute symptoms often improve substantially with immunotherapy, many patients experience persistent memory dysfunction, psychiatric symptoms, or both. Our study provides a neuroimaging framework that is sensitive to this long-term morbidity and captures patient-specific brain changes, offering new possibilities for biomarker-based treatment evaluation and post-acute monitoring. Previous evidence has suggested that the psychopathology of NMDAR encephalitis might be best described as a mixed mood-psychosis syndrome. Our study adds a temporal dimension to this model, in which psychosis represents the predominant feature at peak illness, whereas mood-related symptoms dominate long-term psychiatric outcomes. This phenotypic shift highlights the importance of recognising and managing long-term affective morbidity in the post-acute care of patients with NMDAR encephalitis. Future studies are needed to examine if the cognitive and psychiatric outcomes observed in the present study are specific to NMDAR encephalitis or to what extent they might similarly apply to other types of autoimmune encephalitis or acquired brain injury more generally.

seizures, autonomic dysregulation, and impaired consciousness, which can be life-threatening and frequently requires intensive care.<sup>1,2</sup> Although substantial advances have been made in managing the acute disease phase,<sup>1,3</sup> our understanding of long-term outcomes remains incomplete.

Although most patients improve with immunotherapy regarding global functional outcomes, long-term recovery is often protracted, and many patients experience substantial residual symptoms for years after disease onset.<sup>4,5</sup> These residual symptoms include persistent memory impairment and psychiatric symptoms, as well as difficulties in resuming

psychosocial function, occupational activities, and overall quality of life.<sup>4–8</sup> Importantly, self-reports by people with lived experience have identified this post-acute symptom burden as a major barrier to convalescence and social reintegration.

Despite this clinical relevance, the neuroanatomical basis of this long-term morbidity remains poorly understood. Notably, routine clinical MRI is frequently unremarkable or unspecific in the acute disease phase, even in critically ill patients.<sup>9</sup> This clinical–radiological paradox has motivated advanced neuroimaging studies to characterise disease-related brain changes beyond overt lesions.

In this context, structural complexity analysis has emerged as a powerful new tool to describe brain morphology from anatomical MRI data.<sup>10,11</sup> Specifically, fractal dimensionality represents a neuroimaging marker of morphological complexity, which yields a quantitative account of brain shape, beyond size-related changes. This approach has shown high sensitivity in capturing age-related changes of brain morphology across the lifespan<sup>11,12</sup> and in detecting structural brain changes across various clinical conditions, including psychiatric and neuro-immunological disorders.<sup>13,14</sup> Despite these promising reports in related conditions, fractal dimensionality has remained unexplored in patients with autoimmune encephalitis. Against this background, we aimed to compare morphological brain complexity between healthy individuals and patients with NMDAR encephalitis; to characterise symptom trajectories from peak illness to the post-acute stage; and to analyse the relationship between structural brain changes and post-acute outcomes.

## Methods

### Study design

In this cross-sectional study, we included patients with NMDAR encephalitis referred to our reference centre at Charité–Universitätsmedizin Berlin, Germany. Data were acquired between July 18, 2011, and March 17, 2021. Study approval was obtained by the institutional ethics committee (EA1/206/10, EA1/095/12, EA1/105/16, and EA4/011/19). Self-reports on post-acute symptoms by individuals with lived experience informed the study design.<sup>8,15</sup>

### Participants

Participants fulfilled current diagnostic criteria<sup>16</sup> and tested positive for NMDAR antibodies in CSF. All patients were in the post-acute stage, defined as having been discharged from acute hospitalisation (considered the acute disease phase) for at least 1 month. Patients were matched (1:1) to healthy control participants for sex and age by use of logistic regression propensity scores and nearest-neighbour matching, as implemented in the MatchIt package (version 4.5.5) for R (version 4.4.0). Absolute standardised mean differences (SMDs) of up to and including 0.1 were considered indicative of successful matching. Exact matching was applied for participants' sex, resulting in identical sex ratios in both groups. Data on sex were self-reported. Ethnicity data were not available. All participants provided written informed consent.

### Procedures

Clinical data were collected from medical records with standardised case report forms. We evaluated the modified Rankin Scale (mRS) and the Clinical Assessment Scale in Autoimmune Encephalitis (CASE), a more disease-specific score developed to capture core symptoms of autoimmune encephalitis that are not fully represented by global functional scales (appendix p 2).<sup>17</sup> The mRS and CASE were scored retrospectively by two investigators

(GC and KW). This approach yielded paired clinical scores, one at peak illness and one at the post-acute visit at which the MRI was performed. Clinical data for mRS scores were available for 69 (99%) of 70 patients at peak illness, and for all 70 patients at the post-acute visit. Data for CASE scores were available for 68 (97%) of 70 patients at peak illness, and for all patients at the post-acute visit.

Given the high prevalence of psychiatric CASE symptoms, we performed psychiatric phenotyping to classify these symptoms at increased clinical granularity. To this end, patients' mental state examinations at peak illness and at the post-acute visit were scored retrospectively by two formally trained researchers (KW and OJB), who independently evaluated the clinical documentation for the presence of the following symptom categories: psychosis, psychomotor symptoms, catatonia, dissociative symptoms, personality changes, manic symptoms, depressivity, affective dysregulation, suicidality or self-harm, anxiety-related symptoms, aggressivity, and impaired impulse control. Data allowed for a further subdivision of psychosis (hallucinations, delusions, paranoia, and other) and psychomotor symptoms (increase vs decrease). Symptoms that did not fit any of the categories were rare, unspecific (predominantly confusion), and omitted from quantitative analyses. The independent evaluations at each timepoint (ie, acute and post-acute stage) were cross-checked by the respective other researcher (with minimal discordance of <0.2%) and subsequently reviewed by two initially blinded researchers (SK and CF). Thus, we obtained two psychiatric symptom matrices (patients×dimensions): one for peak illness and one for post-acute visits. These matrices respectively underwent hierarchical clustering with Euclidean dissimilarity and Ward linkage. Qualitative cluster assignments in the resulting dendrograms were supported by the silhouette criterion and the Calinski–Harabasz index, which convergently indicated  $k=2$  (peak illness) and  $k=4$  (post-acute stage) as optimal cluster numbers. Details on symptom scoring and cluster analysis are provided in the appendix (p 3).

Given that CASE scoring of memory symptoms is relatively coarse, based on an ordinal scale, and does not differentiate between different memory domains, we additionally analysed patients' memory performance at the time of MRI through standardised neuropsychological examination. Specifically, visuospatial memory was evaluated with the Rey–Osterrieth Complex Figure (ROCF) test (immediate recall and delayed recall),<sup>18</sup> and verbal episodic memory was assessed with the German edition of the Rey Auditory Verbal Learning Test (RAVLT; sum score, post-interference trial, and delayed recall).<sup>19</sup> Besides analysing raw values, we conducted a normative interpretation of memory performance based on the respective delayed recall scores. To this end, individual scores were converted into percentile ranks with age-specific norms. Following neuropsychological consensus guidelines,<sup>20</sup> values below the 25th percentile were

labelled as low performance and those at or above the 75th percentile were labelled as high performance.

For neuroimaging analyses, anatomical MRI data were acquired with a 3T Trim Trio scanner (Siemens, Erlangen, Germany) at the Berlin Center for Advanced Neuroimaging. High-resolution T1-weighted images were obtained with a magnetisation-prepared rapid gradient echo sequence and processed with comprehensive FreeSurfer reconstruction (Laboratories for Computational Neuroimaging, Athinoula A Martinos Center for Biomedical Imaging, Charlestown, MA, USA). Regions of interest were based on the Desikan-Killiany Atlas, and global parcellations of cortical grey matter and cerebral white matter were derived by use of voxel index supersets. Volumetric segmentations underwent region-wise structural complexity analysis. Specifically, fractal dimensionality was estimated from the spatial scaling properties of the corresponding segmentation mask<sup>10,11</sup> by use of the openly available *calcFD* toolbox for MATLAB (MathWorks, Natick, MA, USA). This procedure yields a single value of fractal dimensionality that quantifies the region's morphological complexity, whereby higher values reflect more irregular shapes.<sup>11</sup> Further details on neuroimaging analyses are provided in the appendix (pp 4–5).

To quantify global changes of brain morphology, we applied a normative modelling framework that compares the fractal dimensionality profiles of individual participants with those of a specified reference population.<sup>11</sup> For clinical neuroimaging studies, this reference population is defined as the age-matched and sex-matched healthy control group,<sup>21</sup> and normative values of fractal dimensionality are computed as the median over these healthy participants. Subsequently, patients' overall change in brain morphology is quantified as the distance between their individual values and this normative reference vector (appendix pp 5–6). As such, we obtain a single deviation index for each patient that summarises how much their individual brain deviates from the healthy reference. This approach features several theoretical advantages. First, the index considers all regions simultaneously, which reduces the high dimensionality of brain space and avoids multiple region-wise testing. Second, it allows for patient-specific deviation patterns because the approach is agnostic to which particular regions drive the deviation in a given individual. Third, increases and decreases jointly contribute to the deviation index, such that it explicitly captures bidirectional deviations that can be easily missed in group-level analyses.

### Statistical analysis

We assessed continuous relationships with product-moment correlations, frequencies with  $\chi^2$  proportion tests, and univariate comparisons between groups with independent-sample *t* tests. Paired clinical scores (mRS and CASE) were compared with signed rank tests. We assessed group differences in structural complexity estimates with a non-parametric permutation test. Effect sizes were computed as Cohen's *d* for parametric

comparisons,  $r_{\text{zval}}$  for non-parametric comparisons, and  $\phi$  coefficients for  $\chi^2$  proportion tests.

Adjustment for multiple comparisons was implemented with the Benjamini-Hochberg procedure to control the false discovery rate (FDR). Missing data were rare and primarily reflected incomplete clinical documentation. We performed all analyses using available cases only; no missing values were imputed. Inspection of missingness patterns did not suggest enrichment for demographic or disease-related factors. Further details on statistical procedures and control analyses are provided in the appendix (pp 6–7).

### Role of the funding source

The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

### Results

We included 70 patients with NMDAR encephalitis and 70 healthy control participants. Given that exact matching was applied for participant sex, both groups comprised 60 (86%) female participants and ten (14%) male participants (SMD 0;  $\chi^2$  0;  $p=1.00$ ;  $\phi$  0 [0–1]; table). Groups were well matched for age, with a mean age of 28.1 years (SD 10.2; range 15.0–67.0) in patients and 29.0 years (9.3; 16.0–65.2) in control participants (SMD –0.09;  $t$  –0.57;  $p=0.57$ ;  $d$  –0.096 [95% CI –0.43 to 0.23]). Most patients were in early adulthood at disease onset (mean age 25.7 years [SD 10.1]). The most common acute manifestations included psychiatric symptoms (67 [97%] of 69 patients with available data), memory dysfunction (63 [91%] of 69), and seizures (53 [78%] of 68). Treatment included first-line (66 [97%] of 68), second-line (39 [58%] of 67), and third-line (three [4%] of 67) immunotherapy as well as anticonvulsive (50 [75%] of 67) and antipsychotic medication (49 [75%] of 65). Post-acute visits including MRI occurred at a median of 22.2 months from disease onset (IQR 8.5–42.5).

Compared with healthy control participants, patients with NMDAR encephalitis showed a characteristic pattern of brain-wide reductions in fractal dimensionality (figure 1). In the cerebral cortex, these reductions clustered bilaterally in the frontal lobe (strongest effect left: caudal middle frontal gyrus:  $Z$  –2.48,  $p_{\text{perm}}=0.0062$ ,  $p_{\text{FDR}}=0.046$ ; right: rostral middle frontal gyrus:  $Z$  –2.85,  $p_{\text{perm}}=0.0024$ ,  $p_{\text{FDR}}=0.037$ ), the temporal lobe (left: entorhinal cortex:  $Z$  –3.17,  $p_{\text{perm}}=0.0012$ ,  $p_{\text{FDR}}=0.037$ ; right: entorhinal cortex:  $Z$  –2.71,  $p_{\text{perm}}=0.0036$ ,  $p_{\text{FDR}}=0.041$ ), and the cingulate (left: isthmus:  $Z$  –3.28,  $p_{\text{perm}}=0.0004$ ,  $p_{\text{FDR}}=0.025$ ; right: posterior cingulate:  $Z$  –2.43,  $p_{\text{perm}}=0.0082$ ,  $p_{\text{FDR}}=0.046$ ; figure 1A). This fronto-cingulo-temporal cluster of reductions in fractal dimensionality was corroborated in global parcellations of cortical grey matter (frontal:  $Z$  –2.21,  $p_{\text{perm}}=0.011$ ,  $p_{\text{FDR}}=0.026$ ; temporal:  $Z$  –2.22,  $p_{\text{perm}}=0.013$ ,  $p_{\text{FDR}}=0.026$ ; cingulate:  $Z$  –3.22,  $p_{\text{perm}}=0.0006$ ,  $p_{\text{FDR}}=0.0036$ ; figure 1A).

For the *calcFD* toolbox see  
<https://github.com/cMadañ/calcFD>

A remarkably similar pattern emerged in cerebral white matter, in which reductions in fractal dimensionality again clustered in the frontal lobe (left: rostral middle frontal:  $Z = -2.43$ ,  $p_{\text{perm}} = 0.0064$ ,  $p_{\text{FDR}} = 0.047$ ; right: medial orbitofrontal:  $Z = -2.51$ ,  $p_{\text{perm}} = 0.0042$ ,  $p_{\text{FDR}} = 0.047$ ), the temporal lobe (left: inferior temporal:

$Z = -2.88$ ,  $p_{\text{perm}} = 0.0022$ ,  $p_{\text{FDR}} = 0.043$ ; right: middle temporal:  $Z = -3.72$ ,  $p_{\text{perm}} < 0.0001$ ,  $p_{\text{FDR}} < 0.0001$ ), and the cingulate (left: isthmus:  $Z = -2.21$ ,  $p_{\text{perm}} = 0.012$ ,  $p_{\text{FDR}} = 0.059$ ; right: posterior cingulate:  $Z = -2.68$ ,  $p_{\text{perm}} = 0.0026$ ,  $p_{\text{FDR}} = 0.043$ ; figure 1B). Global parcellations of cerebral white matter similarly supported this spatial pattern of reductions (frontal:  $Z = -2.06$ ,  $p_{\text{perm}} = 0.0200$ ,  $p_{\text{FDR}} = 0.0400$ ; temporal:  $Z = -2.34$ ,  $p_{\text{perm}} = 0.0068$ ,  $p_{\text{FDR}} = 0.0204$ ; cingulate:  $Z = -2.64$ ,  $p_{\text{perm}} = 0.0028$ ,  $p_{\text{FDR}} = 0.017$ ; figure 1B). Additionally, patients showed reduced fractal dimensionality in deep grey matter areas and infratentorial regions. The most pronounced reductions across the whole brain were observed in the hippocampus bilaterally (left:  $Z = -3.82$ ,  $p_{\text{perm}} < 0.0001$ ; right:  $Z = -4.54$ ,  $p_{\text{perm}} < 0.0001$ ;  $p_{\text{FDR}} < 0.0001$  for both; figure 1C), and these effects were particularly pronounced in the CA1 subregion, dentate gyrus, and molecular layer (appendix p 10). Mapping these structural changes onto functional networks showed that reductions in fractal dimensionality clustered in several higher-order systems (mesolimbic, ventral attention and salience, default mode, frontoparietal), whereas primary systems were comparatively less affected (appendix p 11). In sum, these analyses showed a characteristic anatomical pattern of reductions in fractal dimensionality, including the hippocampus bilaterally and a fronto-cingulo-temporal cluster in grey matter and white matter.

Regarding clinical outcomes, patients were severely affected at peak illness (median mRS 5 [IQR 3–5]; median CASE 11 [6–15]), but showed significant improvement in both mRS (median 1; peak illness vs post-acute visit  $Z = -7.2$ ;  $p < 0.0001$ ;  $r_{\text{zval}} = -0.62$ ) and CASE (median 1;  $Z = -7.2$ ;  $p < 0.0001$ ;  $r_{\text{zval}} = -0.62$ ; figure 2A) at the post-acute visit. However, there was considerable variance in post-acute CASE scores: 23 (33%) of 70 patients scored 0 on all CASE domains, whereas 47 (67%) patients showed a varying degree of residual symptoms at the time of MRI, which was not explained by age ( $r = 0.17$  [95% CI  $-0.07$  to  $0.39$ ];  $p = 0.16$ ) or time since disease onset ( $r = -0.02$  [ $-0.26$  to  $0.21$ ];  $p = 0.84$ ).

Therefore, we hypothesised that the extent of these symptoms would be related to more pronounced brain changes. Normative modelling revealed a significant positive association between the fractal dimensionality deviation index and CASE scores at the post-acute visit ( $r = 0.47$  [95% CI  $0.26$  to  $0.64$ ];  $p < 0.0001$ ; figure 2A), such that patients with higher residual symptom burden also showed stronger structural brain changes. This relationship persisted in a general linear model controlling for age at disease onset, sex, time delay to first treatment, application of second-line or third-line therapy, disease duration, and relapse history ( $\beta$  estimate  $1.00$  [95% CI  $0.50$  to  $1.50$ ];  $p = 0.0002$ ;  $\eta^2_p = 0.22$ ; appendix p 12).

Therefore, we studied which of the CASE subdomains drive these residual symptoms (figure 2B). At peak illness, patients were affected across all subdomains, with psychiatric symptoms, memory dysfunction, and

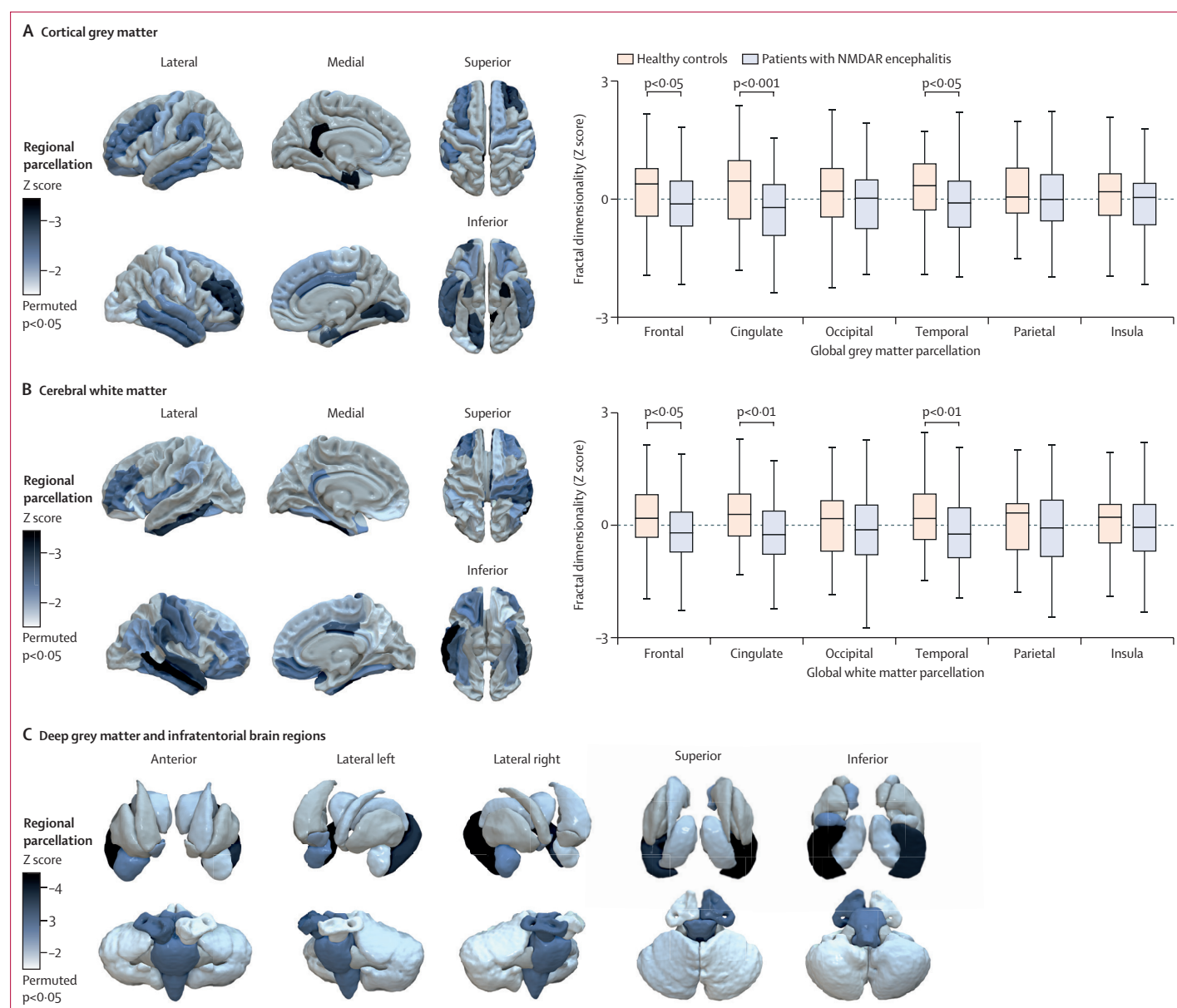
| Patients with NMDAR encephalitis (n=70)    |                    |
|--------------------------------------------|--------------------|
| <b>Demographics</b>                        |                    |
| Mean age at disease onset, years           | 25.7 (10.1; 14–67) |
| Mean age at MRI, years                     | 28.1 (10.2; 15–67) |
| Sex                                        |                    |
| Female                                     | 60 (86%)           |
| Male                                       | 10 (14%)           |
| Clinical presentation in acute stage       |                    |
| Prodromal symptoms                         | 33/66 (50%)        |
| Memory dysfunction                         | 63/69 (91%)        |
| Psychiatric symptoms                       | 67/69 (97%)        |
| Seizures                                   | 53/68 (78%)        |
| Sleep disturbance                          | 37/59 (63%)        |
| Movement disorders                         | 35/66 (53%)        |
| Autonomic dysfunction                      | 32/69 (46%)        |
| Impaired higher-order cognition            | 62/66 (94%)        |
| <b>Treatments</b>                          |                    |
| Time from disease onset to treatment, days | 31 (14–164)        |
| First-line therapy                         | 66/68 (97%)        |
| Intravenous steroids                       | 44/68 (65%)        |
| Plasmapheresis                             | 33/68 (49%)        |
| Immunoadsorption                           | 12/68 (18%)        |
| Intravenous immunoglobulins                | 29/68 (43%)        |
| Second-line therapy                        | 39/67 (58%)        |
| Rituximab                                  | 27/67 (40%)        |
| Cyclophosphamide                           | 8/67 (12%)         |
| Sustained oral steroids                    | 6/67 (9%)          |
| Azathioprine                               | 5/67 (7%)          |
| Methotrexate                               | 3/67 (4%)          |
| Third-line therapy                         | 3/67 (4%)          |
| Bortezomib                                 | 3/67 (4%)          |
| Anticonvulsive medication                  | 50/67 (75%)        |
| Antidepressant medication                  | 22/66 (33%)        |
| Antipsychotic medication                   | 49/65 (75%)        |
| Time from disease onset to MRI, months     | 22.2 (8.5–42.5)    |
| <b>Outcomes</b>                            |                    |
| mRS score at peak illness                  | 5 (3–5)            |
| mRS score at MRI                           | 1 (1–2)            |
| CASE sum score at peak illness             | 11 (6–15)          |
| CASE sum score at MRI                      | 1 (0–2)            |
| Relapse                                    | 9/68 (13%)         |

Data are mean (SD; range), n (%), n/N (%), or median (IQR). For n/N (%), denominators reflect the number of participants with available data. NMDAR=N-methyl-D-aspartate receptor. mRS=modified Rankin Scale. CASE=Clinical Assessment Scale for Autoimmune Encephalitis.

**Table: Clinical characteristics of patients with NMDAR encephalitis**

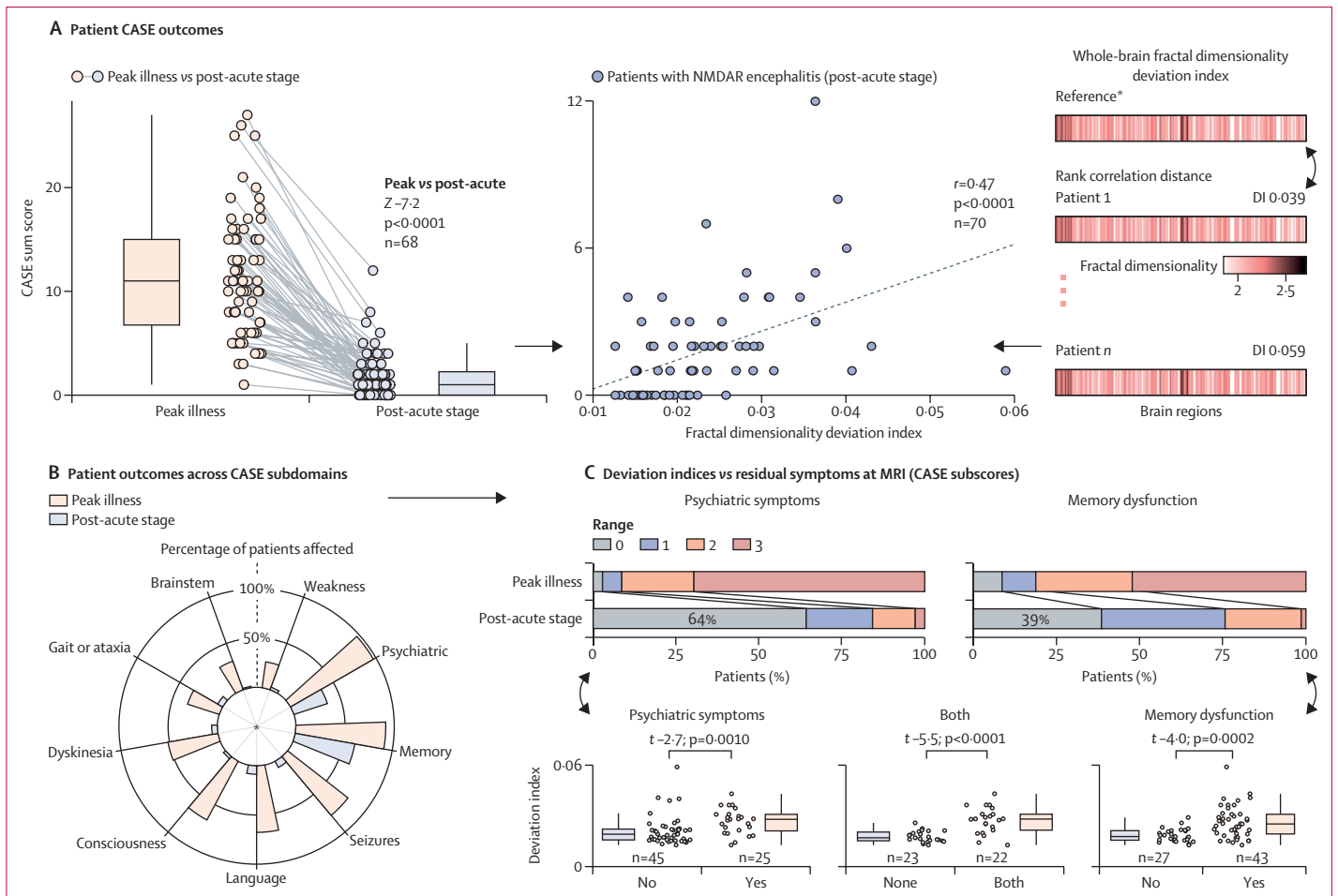
seizures representing the most prevalent symptoms (table). By contrast, residual symptoms at the post-acute visit were largely confined to persistent memory dysfunction (43 [61%] of 70 patients) and psychiatric symptoms (25 [36%] of 70), whereas all other CASE domains had decreased substantially (<10%; figure 2B). Accordingly, we focused on these two leading domains specifically and stratified patients into subgroups based on whether they showed persistent symptoms at MRI or not (figure 2C). This subgroup analysis showed significantly stronger brain alterations in patients with

persistent psychiatric symptoms than in those without ( $t -2.65$ ;  $p=0.0100$ ;  $d -0.66$  [95% CI  $-1.16$  to  $-0.16$ ]; figure 2C). Similarly, we observed stronger brain alterations in patients with persistent memory dysfunction than in those without ( $t -3.98$ ;  $p=0.0002$ ;  $d -0.98$  [ $-1.48$  to  $-0.47$ ]; figure 2C). Notably, the strongest brain changes were observed in patients with both memory dysfunction and psychiatric symptoms relative to those without any residual CASE symptoms ( $t -5.46$ ;  $p<0.0001$ ;  $d -1.63$  [ $-2.29$  to  $-0.95$ ]; figure 2C). These brain changes were not driven by differences in



**Figure 1: Differences in fractal dimensionality between patients with NMDAR encephalitis and healthy control participants**

(A) Differences in regional and global parcellations of cortical grey matter. Regional parcellation is based on the Desikan-Kiliany Atlas. (B) Differences in regional and global parcellations of cerebral white matter. (C) Differences in deep grey matter and infratentorial regions.  $p$  values were derived from non-parametric permutation tests. Effects are thresholded to univariate permuted  $p<0.05$ ; FDR-thresholded brain maps are provided in the appendix (p 9). NMDAR=N-methyl-D-aspartate receptor.



**Figure 2: Association between CASE outcomes and structural brain changes in patients with NMDAR encephalitis**

(A) Patient CASE sum scores (possible range 0–27) at peak illness and post-acute visit (left panel). Scores were compared with a Wilcoxon signed rank test. MRI recordings underlying the imaging analyses were obtained at the post-acute visit. Normative modelling yielded a whole-brain fractal dimensionality deviation index for each patient, derived from comparing the patient brain with the reference population of healthy control participants (right panel).<sup>11,19</sup> The association between this index and post-acute CASE sum scores is illustrated in the middle panel. (B) Patient outcomes across CASE subdomains. The polar plot shows the percentage of affected patients at peak illness and post-acute visit. (C) Fractal dimensionality deviation indices vs residual symptoms at MRI for the two most prevalent CASE subdomains: psychiatric symptoms and memory dysfunction. Symptoms are scored from 0 (none) to 3 (most severe). Subgroup comparisons of patients with and without residual psychiatric symptoms (left), with and without residual memory dysfunction (right), and with both residual psychiatric and memory symptoms versus patients without any residual CASE symptoms (ie, sum score 0; middle). CASE=Clinical Assessment Scale in Autoimmune Encephalitis. DI=deviation index. NMDAR=N-methyl-D-aspartate receptor. \*Median values over healthy controls.

age at disease onset, sex, peak disease severity, time delay to first treatment, ongoing immunotherapy, time since onset, or relapse history (appendix p 12). Similarly, these effects were not explained by age or sex differences among patients with and without residual symptoms (appendix p 8). Furthermore, the relationship between brain changes and post-acute symptoms persisted in a logistic regression approach controlling for age at onset, sex, neurotropic medication at MRI (antidepressant, antipsychotic, anticonvulsive), disease duration, and relapse history (psychiatric symptoms: odds ratio 2.21 [95% CI 1.16–4.98],  $p=0.029$ ; memory dysfunction: 10.15 [3.07–57.15],  $p=0.0014$ ; both 2.61 [1.29–6.44],  $p=0.017$ ).

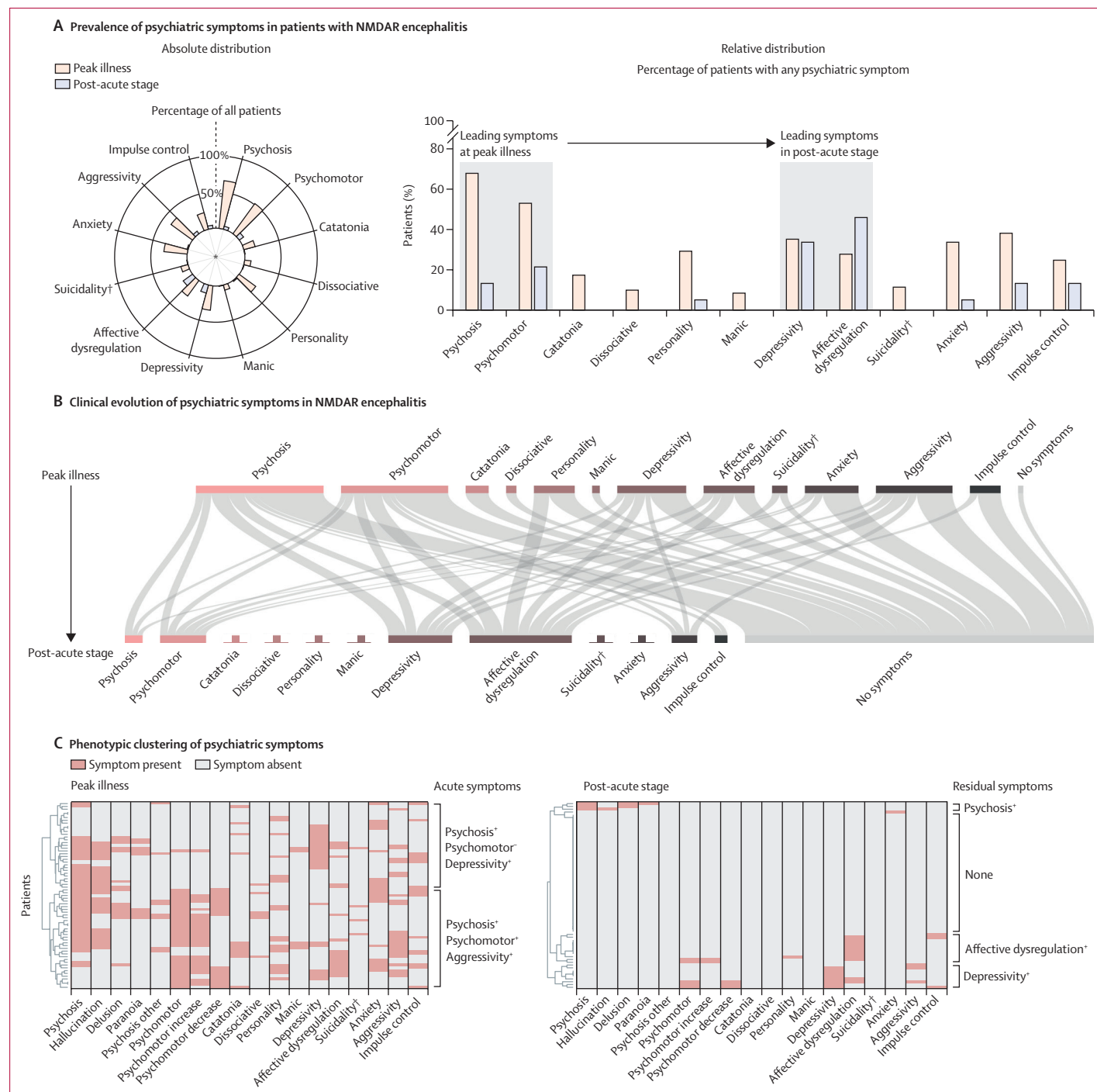
Given their link to these structural brain changes, we additionally analysed patients' psychiatric symptoms

across twelve more granular clinical domains. Psychosis was the leading symptom at peak illness (45 [66%] of 68 patients), followed by psychomotor symptoms (35 [51%]), aggressivity (25 [37%]), depressivity (23 [34%]), anxiety (22 [32%]), and personality changes (19 [28%]; figure 3A). By contrast, the leading residual symptom in the post-acute stage was affective dysregulation (11 [16%] of 69 patients), which predominantly included emotional lability and, to a lesser extent, affective flattening, followed by depressivity (8 [12%]). However, psychiatric symptoms had resolved completely in more than half of the patients at the post-acute visit; therefore, we additionally examined the relative symptom distribution across patients with any psychiatric symptom at each timepoint. This distribution confirmed psychosis and psychomotor symptoms as the

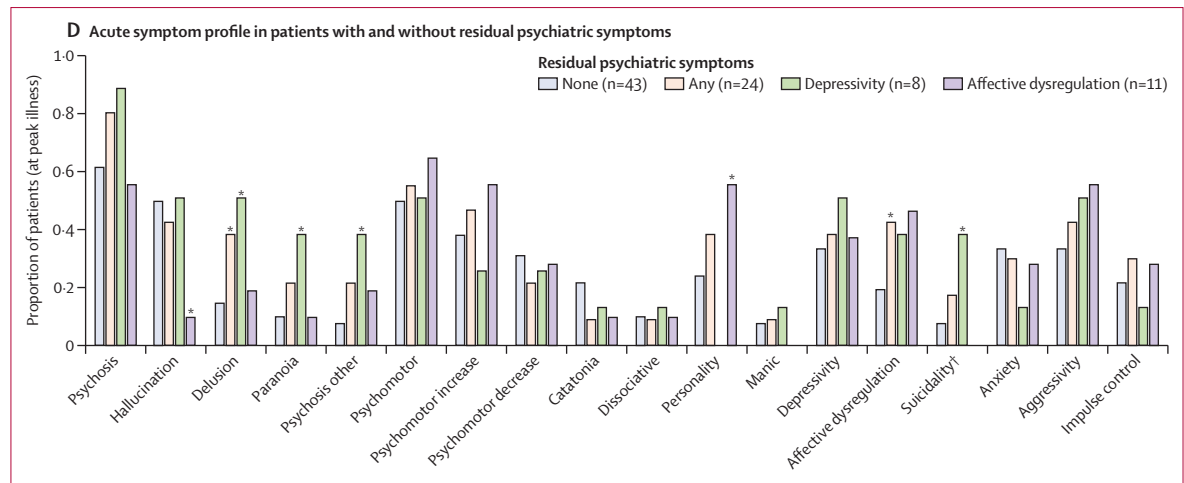
leading symptoms in the acute phase and revealed a shift towards depressivity and affective dysregulation as the leading residual symptoms in the post-acute stage, where the relative occurrence remained stable for depressivity and even increased for affective dysregulation (figure 3A). At the group level, psychiatric manifestations of NMDAR encephalitis thus shifted

from an acute psychosis-dominant phenotype to a residual affective-dominant phenotype.

By studying symptom trajectories from peak illness to the post-acute stage, we observed that patients generally showed improvement across all symptom domains; some symptoms (eg, catatonia, dissociation, or manic symptoms) resolved completely in all patients;



(Figure 3 continues on next page)



**Figure 3: Phenotypic shift of psychiatric symptoms in patients with NMDAR encephalitis**

(A) Absolute distribution of psychiatric symptoms at peak illness and post-acute visit, estimated over all patients (left). Relative distribution of psychiatric symptoms at peak illness and post-acute visit, estimated over patients with any psychiatric symptom at each timepoint (right). (B) Clinical evolution of psychiatric symptoms from peak illness to the post-acute stage. The Sankey plot is thresholded to values greater than one (ie, links representing only one patient are omitted). (C) Phenotypic clustering of symptom matrices at peak illness and post-acute visit. Signs indicate a qualitative description of symptom presence (+) or absence (-). (D) Distribution of acute symptoms in patients with and without residual psychiatric symptoms in the post-acute stage. Proportion tests were conducted relative to the subgroup without residual symptoms. NMDAR=N-methyl-D-aspartate receptor. \* $p<0.05$ . †Suicidality includes suicidal behaviour, ideation, and clinically reported self-harming tendencies.

and residual depressivity and affective dysregulation did not typically persist through the acute phase, but rather developed from a wide spectrum of other acute symptoms (figure 3B). Therefore, we studied whether symptom domains coexisted in the same patients or reflected distinct clinical subgroups. Phenotypic cluster analysis revealed two distinct clinical groups at peak illness: one with low prevalence of psychomotor symptoms and high depressivity, and another with high prevalence of psychomotor symptoms and aggressivity, whereas both showed a high prevalence of psychosis (figure 3C). Conversely, in the post-acute stage, symptom clustering suggested four phenotypic groups, where the largest cluster represented patients without any residual psychiatric symptoms. However, we also observed one small cluster of residual psychosis and two larger clusters characterised by residual depressivity and affective dysregulation, respectively (figure 3C). Notably, nearly all of these patients showed either residual depressivity or affective dysregulation, but not both, suggesting that these symptoms might represent two distinct residual subgroups. Consequently, we investigated whether the distribution of acute symptoms differed between patients with residual symptoms and those without and observed that patients with residual depressivity had presented with significantly increased rates of suicidality, delusions, paranoia, and other psychotic symptoms (predominantly thought disorders) in the acute phase (figure 3D). By contrast, patients with residual affective dysregulation were characterised by significantly reduced rates of hallucinations, and increased rates of personality changes in the acute phase (figure 3D).

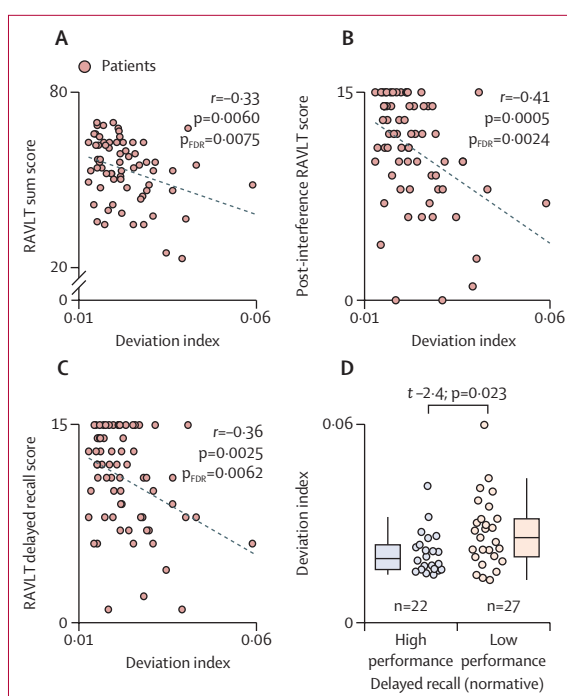
Furthermore, we analysed patients' memory performance at the post-acute visit (appendix p 13) and observed substantial variability in visuospatial and verbal memory scores. Age-specific normative interpretation showed that patients were less affected in the domain of visuospatial memory, with only 13 (20%) of 66 patients with available data meeting the low-performing criterion (<25th percentile of normative reference), whereas 27 (40%) of 68 patients fulfilled this criterion for verbal memory ( $\chi^2 6.40$ ;  $p=0.011$ ;  $\phi 0.22$  [95% CI 0.08–1.00]), suggesting that persistent memory symptoms were domain-specific, with verbal memory more affected than visuospatial memory. We therefore hypothesised that patients with lower post-acute memory performance would show stronger brain changes, and that this effect would be more pronounced for verbal than for visuospatial memory. In line with this hypothesis, lower verbal memory performance was associated with higher fractal dimensionality deviation indices, and this was consistently observed for the RAVLT sum score ( $r -0.33$  [95% CI  $-0.53$  to  $-0.10$ ];  $p=0.0060$ ;  $p_{FDR}=0.0075$ ; figure 4A), interference trial ( $r -0.41$  [ $-0.59$  to  $-0.19$ ];  $p=0.0005$ ;  $p_{FDR}=0.0024$ ; figure 4B), and delayed recall ( $r -0.36$  [ $-0.55$  to  $-0.13$ ];  $p=0.0025$ ;  $p_{FDR}=0.0062$ ; figure 4C). Additionally, a subgroup analysis based on normative references revealed stronger brain changes in patients who fulfilled the low-performing criterion than in those who fulfilled the high-performing criterion in the RAVLT ( $t -2.35$ ;  $p=0.023$ ;  $d -0.68$  [95% CI  $-1.24$  to  $-0.10$ ]; figure 4D; appendix p 13). We observed similar effects for visuospatial memory, albeit with slightly lower effect sizes: stronger brain changes were associated with lower ROCF scores, both for immediate

recall ( $r = -0.30$  [95% CI  $-0.51$  to  $-0.06$ ];  $p = 0.014$ ;  $p_{FDR} = 0.014$ ) and delayed recall performance ( $r = -0.35$  [ $-0.55$  to  $-0.12$ ];  $p = 0.0037$ ;  $p_{FDR} = 0.0062$ ). Furthermore, patients who fulfilled the low-performing criterion in the ROCF showed stronger brain changes than did those who fulfilled the high-performing criterion ( $t = -2.03$ ;  $p = 0.048$ ;  $d = -0.66$  [95% CI  $-1.30$  to  $-0.02$ ]). For both verbal and visuospatial memory, these effects were not driven by age or sex differences between patients who fulfilled the low-performing criterion and those who fulfilled the high-performing criterion (appendix p 8).

## Discussion

This study combined multimodal clinical phenotyping and advanced neuroimaging to show that post-acute outcomes of NMDAR encephalitis are linked to long-term changes in brain structure. Leveraging the framework of fractal dimensionality analysis, we observed that the brains of patients showed systematic reductions in morphological complexity; these reductions followed a characteristic spatial pattern including the hippocampus and a fronto-cingulo-temporal cluster in grey and white matter; two-thirds of patients showed persistent symptoms, despite immunotherapy and good overall recovery; memory dysfunction and psychiatric symptoms represented the most common residual symptoms; in patients with residual symptoms, psychiatric manifestations shifted from a psychosis-dominant phenotype at peak illness to an affective-dominant phenotype in the post-acute stage; and patients with persistent symptoms showed more pronounced brain changes than those without. Collectively, these findings advance our understanding of NMDAR encephalitis along four key directions.

First, the brains of patients showed systematic reductions in morphological complexity, which can be interpreted as a simplification of the brain's geometry. Notably, the complexity of a structure is mathematically distinct from its size, enabling fractal dimensionality to detect subtle structural changes beyond size-related brain measures, such as volume.<sup>11,12,22</sup> Overall, the strongest reductions in fractal dimensionality were observed in the hippocampus, corroborating its role as a primary disease target and extending previous reports of hippocampal volume reductions,<sup>23,24</sup> impaired microstructural integrity,<sup>23,25</sup> surface deformations,<sup>24</sup> and disrupted functional connectivity of the hippocampus<sup>26–29</sup> in NMDAR encephalitis. Additionally, we identified a fronto-cingulo-temporal cluster of fractal dimensionality reductions in grey matter and white matter. This white matter pattern is consistent with fronto-temporal damage in late-myelinating superficial white matter<sup>30</sup> and impaired cingulate integrity,<sup>26</sup> and is biologically supported by previous evidence of NMDAR antibody-mediated oligodendrocyte dysfunction<sup>31</sup> and a connection between white matter fractal dimensionality and early-life myelin maturation.<sup>11</sup> In the cortex, fractal dimensionality



**Figure 4: Association between structural brain changes and patients' memory performance at the post-acute visit**

Verbal episodic memory performance was assessed with the RAVLT. Associations between the fractal dimensionality deviation index and patients' RAVLT sum scores (A), post-interference performance (B), and delayed recall scores (C). (D) Subgroup analysis comparing patients who met the high-performing criterion ( $\geq 75$ th percentile of their age-specific normative reference) and those who met the low-performing criterion ( $< 25$ th percentile) in the delayed recall scores (appendix p 13). RAVLT=Rey Auditory Verbal Learning Test.

identified alterations in frontal and temporal areas, where NMDAR density is thought to be particularly high<sup>32</sup> and previous size-based methods have yielded inconsistent results.<sup>26,33–35</sup> Furthermore, our results highlight the cingulate cortex as an under-recognised disease target with well-established roles in memory function and affective processing,<sup>36</sup> the two leading domains of residual symptoms in our patient population.

Second, patients with persistent psychiatric symptoms showed more pronounced brain changes than those without. At peak illness, psychiatric manifestations represented the leading CASE domain, affecting almost all patients. In the post-acute stage, these symptoms had resolved in approximately two-thirds of the population, whereas a third of patients showed persistent psychiatric morbidity after immunotherapy.

Regarding individual psychiatric symptom trajectories, the symptom domains in our study align with those reported in a large-scale analysis of psychopathology in NMDAR encephalitis, which found that core aspects of mood disorders and psychosis consistently coexist in these patients.<sup>37</sup>

Our study corroborates this mixed mood-psychosis syndrome and shows that psychiatric symptoms dynamically evolve from a psychosis-dominant phenotype

at peak illness to an affective-dominant phenotype in patients with persistent psychiatric morbidity in the post-acute stage. This temporal progression is particularly interesting given recent evidence that mood-related symptoms often precede the onset of psychosis by a few days in the initial disease phase.<sup>38</sup> In light of our findings, affective symptoms thus seem to dominate the very early and the post-acute psychopathology of NMDAR encephalitis (although specific acute and post-acute symptoms might differ), whereas psychosis-dominant manifestations might be largely confined to peak illness.

In this context, there is an ongoing discussion on the transdiagnostic relationship between NMDAR encephalitis and schizophrenia, based on partially overlapping clinical features and disrupted glutamatergic signalling as a potential shared pathological mechanism.<sup>39</sup> Regarding disease onset, it has been recognised that the psychopathology of acute NMDAR encephalitis is systematically distinct from primary psychosis, including ultra-rapid onset (<7 days), phenotypic complexity, and dynamic temporal evolution as distinctive features.<sup>38</sup> Nonetheless, a prospective outcome study found that cognitive and psychiatric symptoms in the early post-acute stage of NMDAR encephalitis can resemble those of stabilised schizophrenia.<sup>6</sup> However, recovery in that cohort was non-linear, with most improvements occurring 4–10 months following hospital discharge. Given the longer disease duration in our study (around 2 years since onset on average), the shift towards affective symptoms might reflect ongoing (and potentially modifiable) disease processes in the subgroup of patients with persistent psychiatric morbidity.

Importantly, both low mood and affective dysregulation featured prominently in a study on patient-reported outcomes of NMDAR encephalitis, in which subjective depressive symptoms were additionally associated with reduced self-reported quality of life.<sup>8</sup> Our results suggest that the presence of certain symptoms at peak illness might indicate an elevated risk for such later psychiatric morbidity. In particular, post-acute depressivity was associated with the presence of delusions, paranoia, thought disorders, and self-harming tendencies in the acute phase, whereas affective dysregulation in the post-acute stage was associated with increased rates of personality changes and, interestingly, reduced rates of hallucinations in the acute stage. These results call for dedicated studies to evaluate such clinical predictors systematically and emphasise the importance of managing affective morbidity in the post-acute care of patients with NMDAR encephalitis.

Third, brain changes were more pronounced in patients with persistent memory dysfunction than in those without. Memory dysfunction was highly prevalent at peak illness and represented the leading CASE symptom in the post-acute stage. These results corroborate previous evidence showing that long-term memory dysfunction is common in patients with

NMDAR encephalitis<sup>4,7,40,41</sup> and represents one of the most important patient-reported concerns.<sup>8</sup>

Additionally, we found that patients with stronger brain alterations performed worse on prospective memory tests (RAVLT and ROCF), wherein verbal episodic memory was comparatively more affected than visuospatial memory. Regarding cognitive outcomes of NMDAR encephalitis, it has been argued that some cognitive domains such as episodic memory might be less likely to recover than others,<sup>41</sup> and a persistent impact on verbal memory was similarly observed in a study on cognitive recovery trajectories.<sup>4</sup> Notably, fractal analysis sensitively detected stronger brain changes in more affected patients across both the broader CASE score of memory dysfunction and the domain-specific memory assessments at MRI.

Fourth, our findings support the view that current treatment strategies do not sufficiently prevent long-term sequelae in many patients with NMDAR encephalitis,<sup>3</sup> highlighting the need for better prognostic markers and improved post-acute monitoring. Our study offers fractal dimensionality as a promising new imaging marker to track clinically relevant brain changes, which yielded several moderate-to-large effect sizes that are similar to previous applications in patients with neurodegenerative disorders.<sup>13,42</sup> Importantly, fractal dimensionality does not require specialised MRI sequences but can be derived from standard three-dimensional T1-weighted images, facilitating its use in future studies and, potentially, as a clinical biomarker. Although further validation regarding scanner hardware, multicentre harmonisation, and external validation cohorts will be necessary before clinical translation, fractal dimensionality has already shown robustness across different scanning sequences<sup>10</sup> and improved test–retest reliability compared with earlier neuroimaging measures.<sup>22</sup> Additionally, our normative modelling framework enables more personalised outcome markers because it explicitly captures patient-specific patterns of brain changes. Besides the present study, this approach has shown high sensitivity in a study on neurodevelopment<sup>11</sup> and a related application in LGI1 encephalitis.<sup>21</sup>

Despite these promising implications, limitations of our study include the cross-sectional design, which precludes inferences on when the observed brain alterations develop. Similarly, disease duration varied because patients were included in the study at referral to our reference centre. Although this variability did not explain residual morbidity in our study, longitudinal assessments are necessary to understand how patient-specific recovery is influenced by individual disease course, comorbidities, or treatment, and to characterise the exact temporal trajectories of the observed phenotype shift. Of note, psychiatric manifestations of NMDAR encephalitis are highly dynamic at disease onset, commonly changing within days,<sup>38</sup> which raises the question of whether affective-dominant symptoms in the

post-acute stage show similar fluctuations or are more stable over time. Regardless, retrospective clinical analyses as applied here might not capture the full complexity of this evolution, highlighting the need for prospective evaluations at higher temporal granularity. Furthermore, our control group consisted of healthy participants, raising the question to what extent the observed changes are specific to NMDAR encephalitis or whether they similarly apply to other forms of autoimmune encephalitis or acquired brain injury more generally.

Overall, the observed link between persistent symptoms and structural brain changes prompts an important general question: what distinguishes patients with persistent morbidity after immunotherapy from those without? One explanation could be that acute NMDAR encephalitis is initially driven by functional alterations related to disrupted glutamatergic signalling, which might help explain the rapid, polymorphic, and fluctuating symptoms at disease onset and, possibly, the clinical–radiological paradox. Such a functional disruption is also consistent with the well-documented alterations of functional connectivity<sup>26,27,43</sup> and increased volatility of brain signals in patients with NMDAR encephalitis.<sup>28,29,44</sup> Over time, however, some patients seem to progress to broader structural brain damage, including the previously reported white matter changes,<sup>26,30,45</sup> hippocampal atrophy,<sup>23</sup> and the macrostructural brain alterations observed in the present study. In turn, these structural changes likely cause secondary functional alterations, yielding a complex interplay of structural damage and functional reorganisation in long-term recovery.

Although the factors underlying individual vulnerability to structural brain damage remain uncertain, potential contributors include genetic predisposition, antibody affinity, immune response, treatment effects, ongoing neuroinflammation, and secondary neurodegeneration.<sup>46</sup> As such, interdisciplinary collaborations and multi-modal data will be essential to test this function-to-structure hypothesis of NMDAR encephalitis and to unravel predisposing factors for long-term brain damage in individual patients. In conclusion, our findings have important implications for understanding the clinical evolution and outcomes of NMDAR encephalitis and highlight fractal dimensionality as a promising imaging marker to capture patient-specific patterns of brain alterations using routine MRI data.

#### Contributors

SK and CF conceptualised the study. SK, GC, WZ, AR, KW, OJB, and SR curated the data. SK, GC, KW, and SR conducted the formal analysis. CF acquired the funding. SK, GC, WZ, KW, OJB, and SR conducted the investigation. SK, KW, OJB, SR, CRM, and CF contributed to methodology. SK and CF were responsible for project administration. HP and CF contributed to resources. SK, AR, and CRM contributed to software development. FP, HP, and CF supervised the study. SK, GC, WZ, KW, OJB, SR, and CF validated the data. SK and AR produced the figures. SK wrote the original draft. All authors reviewed and edited the manuscript. SK, GC, WZ, KW, OJB, SR, and CF directly accessed and

verified the data. All authors had full access to all the data in the study and had final responsibility for the decision to submit for publication.

#### Declaration of interests

FP has received honoraria or consulting fees from Alexion, Amgen, AptaTherapeutics, Bayer, CRISPR Therapeutics, Merck, Novartis, Oculis, Roche, Sandoz, Teva, Toleris, and UCB; and serves on scientific advisory boards for Novartis and Roche. All other authors declare no competing interests.

#### Data sharing

De-identified aggregate data are available after publication upon reasonable request to the corresponding author, pending a data sharing agreement. Resources supporting the findings of this study are available on the Open Science Framework (<https://osf.io/b28cp>).

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