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Superficial white matter damage in anti-NMDA receptor encephalitis

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Abstract

Background—Structural brain MRI is normal in the majority of patients with Anti–N-methyl-D-aspartate receptor (NMDAR) encephalitis. However, extensive deep white matter damage has recently been shown in these patients. Here, our aim was to study a particularly vulnerable brain compartment, the late-myelinating superficial white matter.

Methods—Forty-six patients with anti-NMDAR encephalitis were included. Ten out of these were considered neurologically recovered (modified Rankin scale of zero), while 36 patients were non-recovered. In addition, thirty healthy controls were studied. MRI data were collected from all subjects and superficial white matter mean diffusivity derived from diffusion tensor imaging was compared between groups in whole brain, lobar, and vertex-based analyses. Patients underwent comprehensive cognitive testing, and correlation analyses were performed between cognitive performance and superficial white matter integrity.

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Results—Non-recovered patients showed widespread superficial white matter damage in comparison to recovered patients and healthy controls. Vertex-based analyses revealed that damage predominated in frontal and temporal lobes. In contrast, the superficial white matter was intact in recovered patients. Importantly, persistent cognitive impairments in working memory, verbal memory, visuospatial memory and attention significantly correlated with damage of the superficial white matter in patients.

Conclusions—Anti-NMDAR encephalitis is associated with extensive superficial white matter damage in patients with incomplete recovery. The strong association with impairment in several cognitive domains highlights the clinical relevance of white matter damage in this disorder and warrants investigations of the underlying pathophysiological mechanisms.

Introduction

Anti–N-methyl-D-aspartate receptor (NMDAR) encephalitis is an autoimmune encephalitis that exhibits a characteristic neuropsychiatric syndrome and has a severe and prolonged clinical course [1]. Clinical routine MRI is normal in most patients, but advanced imaging analyses, including resting state fMRI, volumetric analyses and diffusion tensor imaging, have identified structural and functional imaging correlates of the disease [2–4]. Recently, we observed a characteristic pattern of whole-brain functional connectivity alterations that correlated with memory impairment and psychiatric symptoms in anti-NMDAR encephalitis [5]. Moreover, extensive white matter changes within the large deep white matter fibers that were shown to correlate with disease severity were described [2]. However, the exact contribution of white matter damage to disease pathophysiology remains elusive. To address this issue, we examined the integrity of the short-range association fibers (U-fibers) and intracortical myelin, which is made up largely of oligodendrocytes, at the interface between cortical gray matter and deep white matter (here called the superficial white matter –see Table 1 for a brief overview) to test links between structural and functional impairment in NMDAR encephalitis. Several lines of evidence support the hypothesis of disease-related damage to the superficial white matter and why it may be linked to functional impairments. First, the superficial white matter is a highly vulnerable area that matures after the deep white matter [6][7,8]. Moreover, the oligodendrocytes in the superficial white matter myelinate axon segments with fewer wraps than in the deep white matter,[9] thus rendering axons more susceptible to impairments [10]. In addition, the superficial white matter has been shown to be especially vulnerable in schizophrenia [11], a disease which shares pathophysiological mechanisms (NMDAR dysfunction), clinical symptoms (including positive and negative symptoms as well as cognitive deficits) and neuroimaging findings (hippocampal atrophy, damage of deep white matter, altered functional connectivity within the fronto-parietal control network and the ventral attention network) with anti-NMDAR encephalitis [2,3].

Importantly, although patients with anti-NMDAR encephalitis frequently suffer from a severe clinical course, many patients respond well to treatment and return to a relatively high level of function [12,13]. Together with recent neuroimaging findings, this suggests that functional impairment and structural damage of the brain in patients with active symptoms may recover substantially. Given its vulnerability, we investigated the superficial white

matter with the hypothesis that it may be adversely affected in patients with ongoing disease activity, but may recover in patients that no longer exhibit symptoms. Furthermore, we investigated a possible relationship between integrity of superficial white matter and cognitive impairment.

Methods

Forty-six patients with anti-NMDAR encephalitis were recruited from the Department of Neurology at Charité - Universitätsmedizin Berlin (age, mean±SD: 26.67±8.45, 40F/6M). All patients had a characteristic clinical presentation [14] and were tested positive for immunoglobulin G NMDAR antibodies using an immunofluorescence cell-based assay expressing recombinant NMDAR. In addition, all patients tested negative for AMPAR, GABA-B-R, LGI1 und CASPR2 antibodies. Similarly, MOG and AQP4 antibodies were not detected (tested in 21/46 patients). The control group comprised 30 healthy subjects without history of neurological or psychiatric disorders (age: 27.53±8.42, 24F/6M). Resting state fMRI, structural MRI, and optical coherence tomography analyses of some patients have previously been reported [2,3,15]. Patients were studied 27.6 ± 4.6 months after symptom onset and 12.1 ± 2.4 months after the end of the last acute care hospitalization. The patient's disease severity was independently assessed at the time of MRI studies by two experienced neurologists using the modified Rankin scale (mRS). Ten patients with an mRS score of 0 were considered clinically recovered (recovered patients, age, 26.60±7.38, 8F/2M;), while 36 patients had residual deficits as indicated by mRS scores > 0 (non-recovered patients, age, 26.69±8.83, 32F/4M; mRS = 1, 15 patients; mRS = 2, 16 patients; mRS = 3, 6 patients). Importantly, the mRS is a general measure of function and does not capture subtle deficits, including mild to moderate cognitive dysfunction, which may still be present. In addition to the mRS at the time of study, the maximal mRS during the acute disease phase was assessed (Table 2). The study was approved by the ethics committee of the Charité - Universitätsmedizin Berlin. All study participants gave written informed consent for research and publication.

Cognitive assessment

All study participants underwent cognitive testing with a comprehensive test battery that covered attention (alertness and divided attention), verbal and nonverbal short-term and working memory (digit span forward and backward, block tapping forward and backward), verbal and visuospatial memory (Rey Auditory Verbal Learning Test [RAVLT] and Rey-Osterrieth Complex Figure Test [ROCF]) and executive function (computerized go/no-go test), as described in detail previously [16].

MRI Data Acquisition

MRI data were acquired on a Siemens Magnetom Tim Trio 3T scanner equipped with a 12-channel phased-array head coil and included the following sequences: (i) 3D 1mm isotropic magnetization-prepared rapid gradient echo (MPRAGE) sequence (TR = 1900 ms, TE = 2.55 ms, TI = 900 ms, flip angle = 9°, FOV = 240 × 240 mm^2, matrix size = 240 × 240, 176 slices, slice thickness = 1 mm) for structural acquisition and (ii) a single-shot echo-planar imaging sequence for diffusion MRI acquisition (TR = 7500 ms, TE = 86 ms, FOV = 240 ×

240 mm^2, voxel size = 2·5 × 2·5 × 2·3 mm^3, 61 slices, 64 diffusion directions, b value = 1000 s/mm^2, 1 b=0 image).

Structural and Diffusion MRI Processing

Detailed processing steps are covered in [17,18] with earlier iterations of the superficial white matter mapping methods covered in [8,11]. The author responsible for MRI data analysis (OP) was blinded to clinical details of subjects. In brief, T1-weighted images were processed using BrainSuite's cortical surface extraction pipeline (http://brainsuite.org/processing/surfaceextraction/ v14b), which produces surface models of the cerebral cortex from T1 MRI.[19] Next, the surfaces for each subject were registered to a reference atlas surface using BrainSuite's surface/volume registration software (SVReg; http://brainsuite.org/processing/svreg/, v14b) [20–22]. Outputs from SVReg were inspected to ensure proper segmentation and surface/volume registration. The Diffusion-weighted images were processed with the BrainSuite Diffusion Pipeline (BDP [23]; http://brainsuite.org/processing/diffusion/). Finally, to allow cross-subject sampling of anatomically comparable superficial white matter mean diffusivity, diffusivity was sampled along each vertex of the white matter surface that had been mapped to the atlas reference via SVReg. Mean diffusivity was chosen to be the focus of this study rather than other diffusion metrics commonly examined in deep white matter investigations (axial and radial diffusivity, fractional anisotropy) given that the difference between axial and radial diffusivity values is considerably smaller in the superficial white matter than in the deep white matter [8,17,18]. Methodological limitations include the inherent difficulty for tissue classification in MRI images and potential partial volume effects, however, these are minimised by the inspection of each tissue-classified image to ensure proper segmentation. Furthermore, we additionally generated a ventricle/CSF and subcortical grey matter mask (including the hippocampus which is not included in BrainSuite's surface model). This image mask was then applied to the diffusivity image. This step was done as an extra quality control measure to maximise sampling of the superficial white matter and to minimise confounds from other areas.

Whole brain mean diffusivity was extracted for each subject and these values were then used to test for differences between groups (Recovered Patients, Non-Recovered Patients, Controls) using SPSS's General Linear Model (GLM) with sex and age as covariates. If a difference between groups was detected at the whole brain level, we followed up within lobar (frontal, temporal, parietal, limbic, occipital) regions of interest (ROIs) to identify where the changes were located. Likewise, for increased spatial resolution, we applied an exploratory GLM (http://brainsuite.org/bss/) [24] at the vertex level for lobar ROIs that were shown to be significantly different between groups to identify precisely where the differences in mean diffusivity were located.

Correlations Between the Superficial White Matter and Cognitive Measures

To investigate whether superficial white matter changes were related to global degree of disability and cognitive scores (verbal memory [RAVLT sum score], visuospatial memory [ROCF delayed recall], attention [mean of z-transformed phasic and tonic alertness performance] and working memory [mean of z-transformed digit span backward and block span backward performance]) we ran a partial correlation analysis including all patients

(both recovered and non-recovered NMDA patients) within SPSS between these measures and whole brain superficial white matter mean diffusivity with sex and age as covariates. If there was a significant effect, we investigated further within lobar ROIs. If there was a significant effect within an ROI we included this region in an exploratory vertex based GLM analysis with sex and age as covariates between the measures and superficial white matter mean diffusivity. Significance threshold was set for all tests at $p<0.05$.

Results

There was no significant difference between recovered and non-recovered patients regarding age (recovered, mean 26.60 ± 7.38 years, non-recovered 26.69 ± 8.83 ± 1.8; p = 0.471), CSF antibody titers (median 3.2 [range 0–10] vs. 3.2 [0–320], p = 0.84), maximal mRS scores (mean 3.8 ± 0.3 vs. 4.2 ± 0.2, p=0.31), disease duration (duration of hospitalisation; mean 84.1 ± 26.0 days vs. 105.6 ± 18.8 days; p = 0.55), time since disease onset (mean 23.9 ± 5.2 months vs. 26.5 ± 4.3 months; p = 0.74), or time between symptom onset and first treatment (mean 224 ± 128 days vs. 155 ± 40 days; p = 0.65). Non-recovered patients had marked cognitive impairment and performed significantly worse than healthy controls in all investigated cognitive domains, i.e. verbal memory, visuospatial memory, working memory, attention and executive function (Table 2). In contrast, recovered patients had normal performance for visuospatial memory, verbal memory and attention and only mild deficits in working memory and attention. No correlation between antibody titers and superficial white matter changes or cognitive function were observed.

Whole Brain Analysis

Whole brain superficial white matter mean diffusivity analysis revealed a significant microstructural integrity impairment in non-recovered patients in comparison to recovered patients (recovered vs. non-recovered, df=45, F=11.62, p=0.001) and healthy controls (non-recovered vs. controls, df=64, F=13.098, p=0.001; Fig. 1). In contrast, no impairment of superficial white matter integrity was observed in recovered patients in comparison to controls (recovered vs. controls, df=38, F=1.944, p=0.172).

Lobar Region-of-Interest Analysis

To explore superficial white matter damage in non-recovered patients in more detail, we performed lobar ROI analyses that showed significant differences between patients and controls within the frontal, temporal, and parietal lobes bilaterally as well as within the left occipital lobe (Table 3; Supplementary Figure 1).

Vertex-Based Analysis

To allow for a more fine-grained anatomical mapping, a precise vertex-based analysis was performed only within the lobar ROIs where there was a significant effect and revealed widespread differences (Fig. 2). In order to quantify which vertices had the largest differences in diffusivity between controls and non-recovered patients, we calculated the percentage difference at each vertex (Fig. 3). Percentage difference maps revealed increased mean diffusivity within the superficial white matter in distributed brain regions most prominently within the frontal, temporal and parietal lobes.

Correlation Analysis within the superficial white matter

Whole brain superficial white matter damage was significantly correlated with disease severity (mRS) and cognitive deficits in verbal memory, visuospatial memory, attention and working memory, i.e., a higher mean diffusivity was associated with a worse performance (Table 4). In order to localize correlations in more detail, we performed lobar ROI analyses, which showed widespread associations in the same direction, i.e., higher mean diffusivity was associated with a worse performance (Table 4). In order to identify precisely which vertices were associated with clinical symptoms within significantly associated lobar ROIs only, we ran vertex-wise correlation analyses (Fig. 4). Verbal memory strongly correlated with superficial white matter damage throughout the brain, but particularly with damage in the temporal lobes bilaterally and the left cingulate, while visuospatial memory was associated with damage bilaterally in the lateral frontal lobes, the left temporal lobe, and left cingulate. Working memory correlated with damage in the bilateral lateral prefrontal regions. Attention correlated with damage predominantly in the occipital lobes bilaterally and in the right parietal lobe. Disease severity (mRS) was associated with superficial white matter damage in the frontal, temporal, parietal, and occipital brain regions (Fig. 4).

Discussion

The aim of this study was to investigate superficial white matter integrity in patients with anti-NMDAR encephalitis. The following main findings emerged from our investigation: (1) there are widespread abnormalities in the superficial white matter of non-recovered patients; (2) recovered patient's superficial white matter showed no abnormalities; (3) superficial white matter integrity is strongly correlated with disease symptoms and disease-related cognitive deficits. Previous brain imaging research on anti-NMDAR encephalitis has demonstrated abnormalities of the long-range deep white matter [2], hippocampus [3], and widespread alteration of functional connectivity with predominant affection of fronto-temporal connections [2]. Our results are in line with these previous findings and additionally demonstrate that there are extensive abnormalities in brain structures that have not been examined previously. Importantly, these abnormalities are closely linked to cognitive impairments.

The observed results clearly indicate that abnormalities of the superficial white matter persist in non-recovered patients. However, the superficial white matter is a complex area and our knowledge of this region is still limited. For example, besides containing cortico-cortical short range connections [11], long range axonal projections also pass through this area [25] and it additionally contains a high proportion of "interstitial neurons" [26]. Volumetrically, the superficial white matter is largely composed of myelin and oligodendrocytes. Indeed, oligodendrocytes express NMDA receptors [27,28], that may result in a vulnerability to antibodies targeting these receptors and loss of myelin sheaths [29]. Together, this suggests that the observable diffusivity changes are driven by changes in oligodendrocytes. These changes could be particularly detrimental because oligodendrocytes in the superficial white matter myelinate up to 50 axon segments with fewer than 10 myelin membrane wraps [9]. These late myelinating oligodendrocytes are thus structurally more complex and metabolically overextended compared to the deep white matter where

oligodendrocytes tend to myelinate only a single axon segment with about 100 wraps [10,30]. This suggests that damage to oligodendrocytes in this region affects greater number of axons segments than in the deep white matter.

The majority of patients with anti-NMDAR encephalitis recover well with prompt diagnosis and immunotherapy, although cognitive deficits may persist [16]. Previous research has linked disease severity and disease duration to the extent of structural damage, e.g., hippocampal atrophy and deep white matter damage, that in turn predicted the severity of persisting cognitive impairments [2,3]. These findings are corroborated by the present study and extended to the superficial white matter: patients that had not fully recovered (mRS > 0) exhibited widespread damage of the superficial white matter, while, in contrast, recovered patients (mRS = 0) showed no damage. Importantly, there were no differences in clinical parameters such as antibody titer, maximal mRS scores or disease duration between recovered and non-recovered patients. This shows that the heterogeneity in disease course and recovery – as assessed using the mRS – cannot be fully explained by these clinical variables. Possible further relevant factors might include differences in NMDAR antibody affinity or differences in the individual susceptibility to white matter damage, e.g., susceptibility of oligodendrocytes to NMDAR dysfunction-mediated pathology. Damage of the superficial white matter was furthermore closely tied to cognitive impairments: diffusivity in the superficial white matter correlated with deficits in attention, working memory, and verbal and visuospatial long-term memory. Overall, these results suggest that superficial white matter damage is reversible in patients that recover. However, this conclusion will need to be confirmed in longitudinal studies with larger patient cohorts. Multimodal longitudinal studies will also help to further elucidate the contribution of different pathologies in anti-NMDAR encephalitis, e.g. hippocampal atrophy, deep white matter damage and superficial white matter damage, to disease symptoms.

In line with previous investigations, we categorized patients with a mRS score of 0 as *recovered* [1,12,13]. Nevertheless, recovered patients showed moderate deficits of working memory and executive function that are not reflected by the mRS and that might well interfere with everyday activities in university or work [16]. These remaining cognitive deficits may indicate subtle superficial white matter changes and/or may indicate that different structural and functional disease mechanisms contribute to the cognitive deficits in anti-NMDAR encephalitis, likely including the previously observed correlation of memory deficits with impaired hippocampal functional connectivity, [2] disrupted functional connectivity within the medial temporal lobe network, and hippocampal atrophy [3].

Dysfunction of NMDA receptors closely links anti-NMDAR encephalitis to current concepts of schizophrenia pathophysiology [31,32]. The glutamate hypothesis of schizophrenia posits that NMDAR hypofunction can induce a hyperdopaminergic state and can cause the major disease symptoms. Importantly, NMDAR antagonists such as phencyclidine and ketamine reliably induce positive and negative schizophrenia symptoms [31,32]. Consequently, anti-NMDAR encephalitis and schizophrenia can have a remarkably similar clinical presentation with hallucinations, psychosis and delusions (positive symptoms), but also deficits of motivation, attention and memory (negative symptoms) [33,34]. In line with this pathophysiological and clinical overlap, there are notable similarities in neuroimaging

findings between the two disorders, including reduced hippocampal volumes, abnormal resting state connectivity, and deep white matter changes [2,3,35]. Extending these observations, our current results in anti-NMDAR encephalitis mirror the impairments of the superficial white matter in schizophrenia [11]. For example, both non-recovered anti-NMDAR encephalitis patients and schizophrenia patients share widespread abnormalities, e.g. in the temporal lobes bilaterally. Furthermore, vertex-based analyses show overlap between the two disorders in many focal locations including the lateral frontal lobes. The similarity of the results might indicate shared pathophysiological mechanisms that led to superficial white matter abnormalities in anti-NMDAR encephalitis and schizophrenia.

Importantly, anti-NMDAR encephalitis presents a unique opportunity to increase our understanding about brain function in general [36], given that our findings illuminate the role of the superficial white matter in cognitive function. Verbal memory scores were linked with superficial white matter diffusivity across the whole brain, while visuospatial long-term memory was linked bilaterally with the frontal lobes as well as the left temporal lobe and cingulate gyrus. These observations are thus in line with recent evidence that challenges the view of a strict lateralization of memory functions [37]. Working memory was closely tied to diffusivity in the frontal lobe bilaterally, corroborating extensive evidence from lesion, electrophysiological and functional MRI studies [38,39]. Similarly, the observed correlation between visuospatial attention deficits and superficial white matter damage in the occipital lobes bilaterally and the right parietal lobe is in line with previous research [40]. This occipital damage might moreover contribute to the recently described visual dysfunction in NMDAR encephalitis patients [15].

Conclusion

The pathophysiological model of anti-NMDAR encephalitis, based on extensive immunocytochemical, physiological, and molecular studies, holds that NMDAR antibodies induce a reversible capping and internalization of NMDAR without complement activation and cell death [41,42]. It might therefore be speculated that the widespread damage to the deep [2] and superficial white matter is the result of a downstream response to neuronal changes. Alternatively or in addition, interference of antibodies with NMDAR receptors on oligodendrocytes might be involved in the widespread impairment of white matter in anti-NMDAR encephalitis. Independent of the exact mechanism still to be discovered, the role of white matter in the disorder seems to be more substantial than estimated previously.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations

NMDAR	Anti–N-methyl-D-aspartate receptor
mRS	modified Rankin scale

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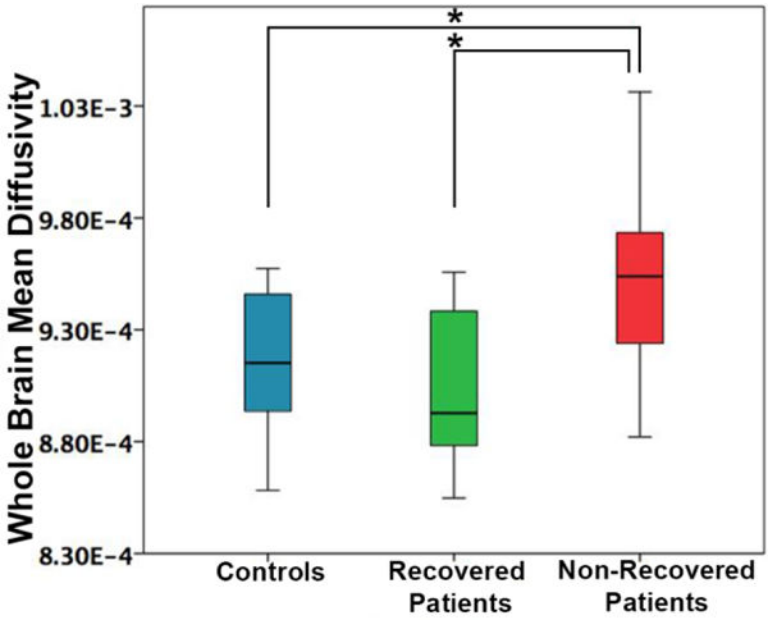

Figure 1. Whole brain superficial white matter mean diffusivity in patients with anti-NMDAR encephalitis and healthy controls

* Indicates significant difference between groups.

There was a significant difference between controls and non-recovered patients ($p < 0.001$) but no significant difference between controls and recovered patients ($p>0.05$). Box plots show the average superficial white matter mean diffusivity value for each group. Mean diffusivity units: $10^{-3}mm^2/s$.

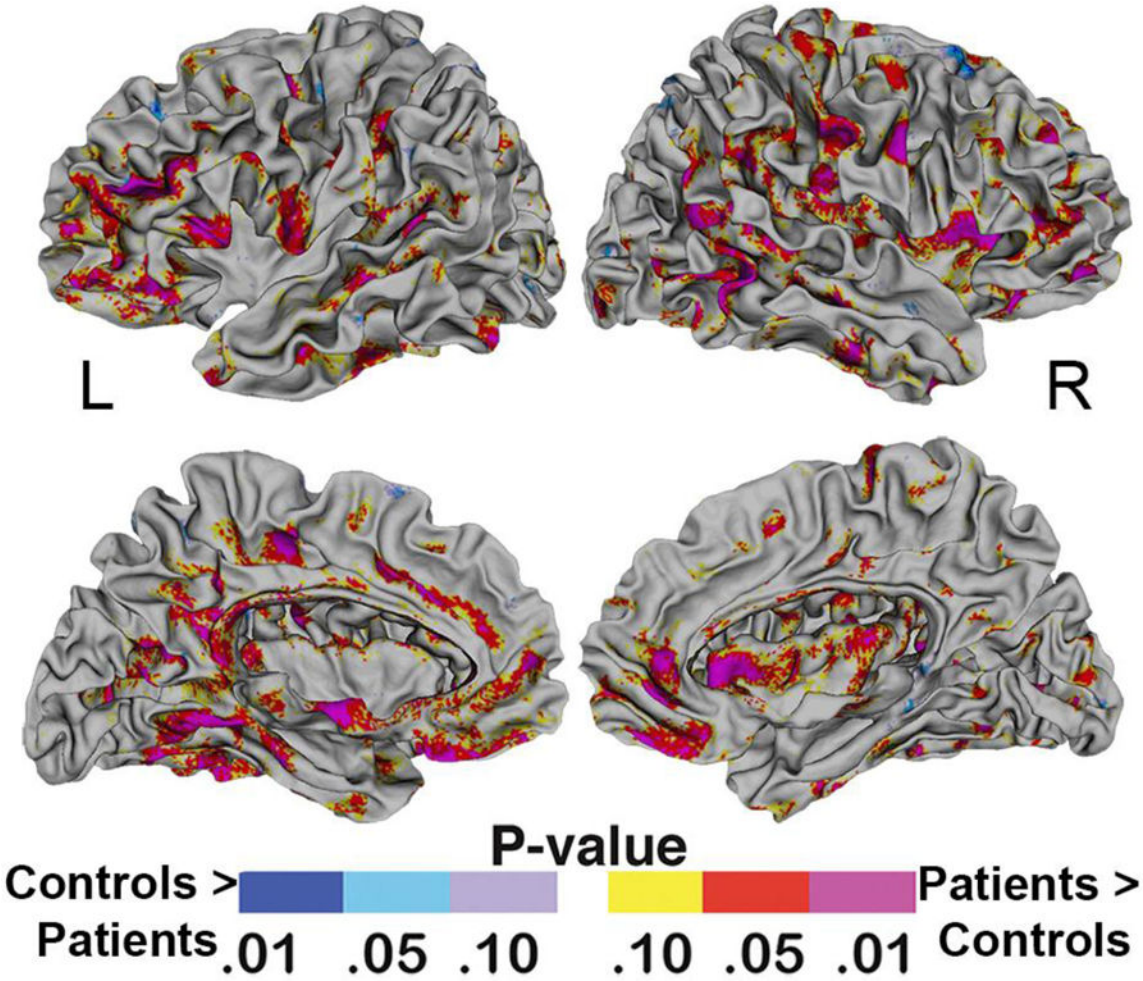

Figure 2. Superficial white matter damage in non-recovered patients with anti-NMDAR encephalitis

Probability maps show effects of NMDAR encephalitis on the superficial white matter (group difference between non-recovered patients and controls): Mean diffusivity controlling for age and gender was mapped at high-spatial resolution at thousands of homologous locations within the superficial white matter. Vertex-based mapping was carried out only in lobar regions where there was a significant difference between non-recovered patients and controls. The direction of effects is indicated by the color bar: purple/red/yellow colors indicate increased diffusivity and cyan/green/blue indicates reduced diffusivity in in non-recovered patients relative to healthy controls.

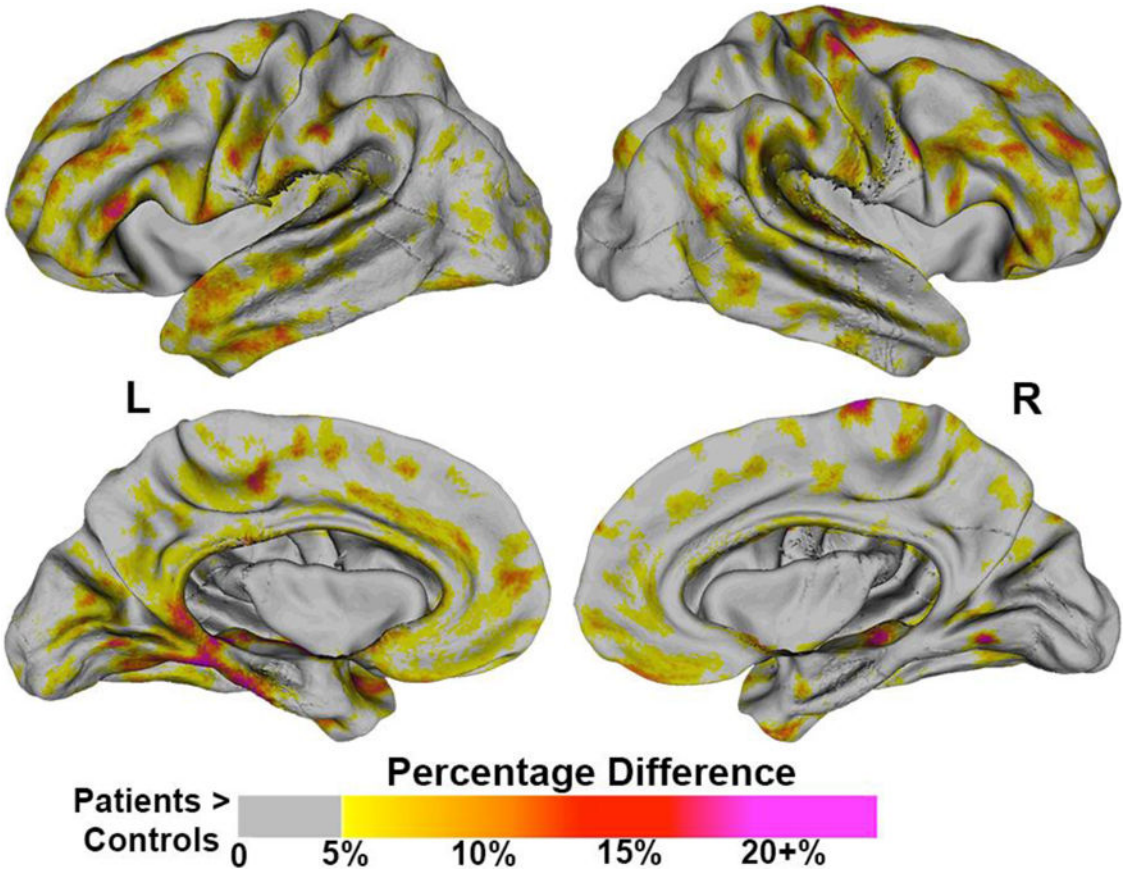

Figure 3. Mean diffusivity percentage difference between non-recovered patients with anti-NMDAR encephalitis and healthy controls

Vertex based percentage difference maps show the difference between non-recovered patients and controls. Heat map color bar indicates percentage difference between the two groups at each vertex point.

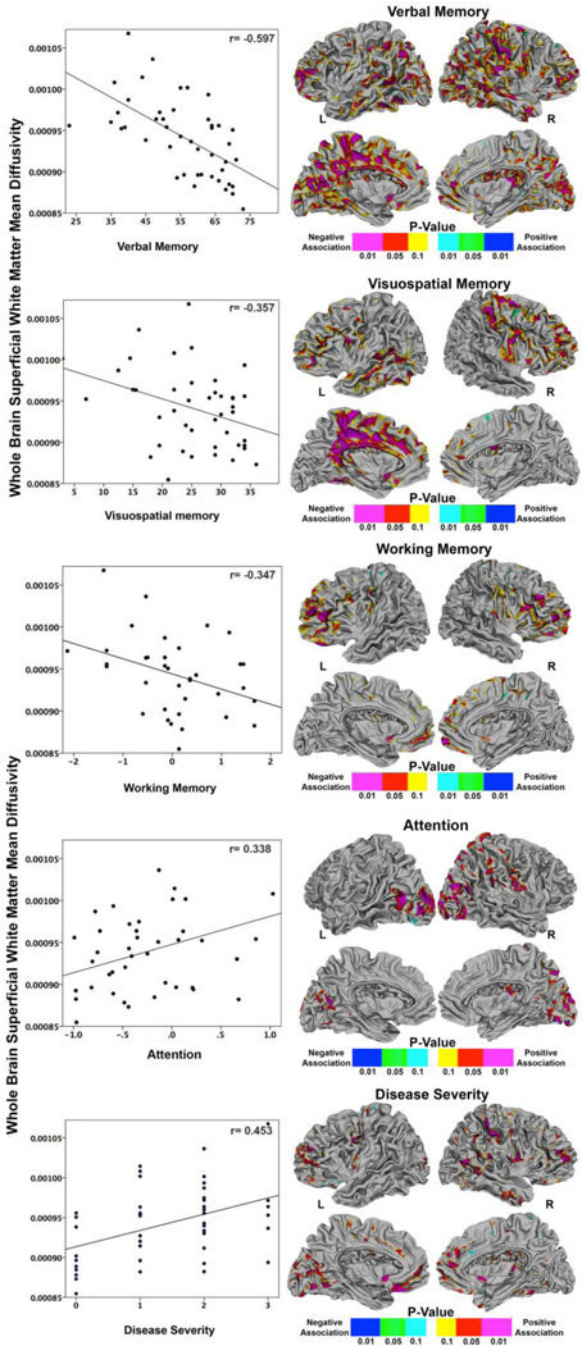

Figure 4. Correlation between superficial white matter damage and cognitive deficits in patients with anti-NMDAR encephalitis

All scatter plots reflect significant correlations between the cognitive domain and whole brain superficial white matter mean diffusivity. Vertex-based mapping was carried out only in lobar regions where there was a significant correlation between the cognitive domains in question (see Table 3). For verbal memory, visuospatial memory and working memory, higher scores indicate better performance; for attention, higher scores indicate worse performance; for mRS, higher scores indicate higher disease severity. In the vertex-based correlation maps, the direction of effects is indicated by the color bar: purple/red/yellow

colors indicate higher diffusivity with worse performance and cyan/green/blue indicates higher diffusivity with a better performance. Correlations included all patients (Recovered and Non-recovered).

Table 1

Differences between superficial and deep white matter.

Superficial White Matter (SWM)	**Deep White Matter**
Short fibers	Long fibers
Small diameter fibers	Larger diameter fibers
Intracortical connections	Intrahemisheric and interhemisheric connections
Late myelinating	Early myelinating compared to SWM
Ogliodendrocytes wrap many axons segments	Ogliodendrocytes wrap few axon segments
Less myelin wraps around the axon	More myelin wraps around the axon
Complex arrangement	Less complex arrangement compared to SWM

Table 2

Sociodemographic and clinical characteristics of patients with anti-NMDAR encephalitis and healthy controls.

	Recovered Patients (n=10)	Non-recovered Patients (n=36)	Controls (n=30)	P value
Gender (male/female)	2/8	4/32	6/24	0.471[w], 1[x], 0.335[y]
Age (years ± SD)	26.6 ± 7.38	26.7 ± 8.83	27.5 ± 8.42	0.359[w], 0.546[x], 0.666[y]
mRS at MRI	0 ± 0	1.75 ± 0.12	NA	0.001[w]
Maximal mRS [*]	3.8 ± 0.3	4.2 ± 0.2	NA	0.31
Verbal Memory [1]	65.5 ± 7.88	53.0 ± 11.7	65.3 ± 7.94	0.003[w], 0.94[x], <0.001[y]
Visuospatial Memory [2]	28.9 ± 5.65	24.18 ± 8.00	27.8 ± 5.12	0.091[w], 0.58[x], 0.041[y]
Working Memory [3]	−0.119 ± 0.507	−0.174 ± 0.864	0.472 ± 0.776	0.850[w], 0.036[x], 0.007[y]
Attention [4]	−0.304 ± 0.418	0.362 ± 1.22	−0.371 ± 0.565	0.099[w], 0.74[x], 0.006[y]
Executive Function [5]	497.6 ± 46.5	525.9 ± 77.5	442.3 ± 66.5	0.303[w], 0.035[x], <0.001[y]

Mean values are reported with the standard deviation. SD = standard deviation; mRS = modified Rankin scale; NA = not available

w =Recovered patients vs non-recovered patients

x = Recovered patients vs controls

y = Non-recovered patients vs controls

[*] Maximal mRS = 5, 21 patients; maximal mRS = 4, 11 patients; maximal mRS = 3, 13 patients; maximal mRS = 2, 1 patient

[1] RAVLT sum score; missing data for 1 non-recovered patient.

[2] ROCF delayed recall; missing data for 3 non-recovered patients.

[3] Working memory composite score; missing data for 1 recovered patients & 9 non-recovered patients.

[4] Alertness score; missing data for 2 non-recovered patients.

[5] Go/NoGo reaction time; missing data for 2 non-recovered patients.

Table 3

Whole brain and lobar superficial white matter mean diffusivity in non-recovered patients with anti-NMDAR encephalitis and healthy controls

	Controls		Non-recovered patients		df=64	
	Mean	**SD**	**Mean**	**SD**	**F**	**p**
Whole Brain	9.18E-04	2.92E-05	9.53E-04	4.37E-05	13.098	**0.001**
Left Frontal	9.12E-04	2.86E-05	9.57E-04	4.93E-05	10.408	**0.002**
Right Frontal	9.14E-04	3.22E-05	9.62E-04	5.15E-05	12.649	**0.001**
Left Temporal	8.50E-04	3.29E-05	8.95E-04	8.20E-05	16.822	**0.001**
Right Temporal	8.75E-04	3.20E-05	9.09E-04	6.25E-05	17.079	**0.001**
Left Parietal	9.52E-04	5.20E-05	9.68E-04	6.89E-05	6.838	**0.011**
Right Parietal	9.57E-04	5.76E-05	9.80E-04	6.28E-05	7.766	**0.007**
Left Limbic	1.00E-03	9.92E-05	1.07E-03	1.29E-04	0.958	0.332
Right Limbic	1.04E-03	9.44E-05	1.06E-03	1.34E-04	3.057	0.085
Left Occipital	9.36E-04	6.18E-05	9.54E-04	7.24E-05	5.601	**0.021**
Right Occipital	9.26E-04	3.71E-05	9.37E-04	5.94E-05	0.321	0.573

*Significant results in bold.

Table 4

Correlations between disease symptoms and superficial white matter integrity.

	Disease Severity		Verbal Memory		Visuospatial Memory		Attention		Working Memory	
	r	**p**	**r**	**p**	**r**	**p**	**r**	**p**	**r**	**p**
Deep White Matter										
Whole Brain	−0.018	0.910	−0.17	0.276	−0.184	0.250	−256	0.116	0.117	0.509
Superficial White Matter										
Whole Brain	0.453	**0.002**	−0.597	**0.001**	−0.357	**0.022**	0.338	**0.016**	−0.347	**0.044**
Left Frontal	0.466	**0.001**	−0.563	**0.001**	−0.347	**0.026**	0.294	0.07	−0.472	**0.001**
Right Frontal	0.48	**0.001**	−0.464	**0.002**	−0.35	**0.025**	0.3	0.064	0.503	**0.001**
Left Temporal	0.251	0.1	−0.336	**0.028**	−0.468	**0.002**	0.276	0.089	−0.215	0.223
Right Temporal	0.316	**0.036**	−0.491	**0.001**	−0.207	0.195	0.23	0.158	−0.212	0.23
Left Parietal	0.246	0.107	−0.441	**0.003**	−0.167	0.296	0.3	0.063	−0.032	0.063
Right Parietal	0.318	**0.035**	−0.547	**0.001**	−0.142	0.374	0.329	**0.041**	−0.329	0.856
Left Limbic	0.262	0.086	−0.405	**0.007**	−0.371	**0.017**	0.249	0.127	−0.149	0.402
Right Limbic	0.026	0.867	−0.045	0.774	0.138	0.39	−0.129	0.433	−0.129	0.433
Left Occipital	0.3	**0.048**	−0.473	**0.001**	−0.233	0.143	0.385	**0.015**	−0.144	0.417
Right Occipital	0.291	0.055	−0.389	**0.01**	−0.107	0.505	0.54	**0.001**	−0.145	0.414

Pearson correlation coefficients and p values for the correlation between disease symptoms and white matter integrity in the whole brain and lobar regions of interest are shown. Correlations included all patients (Recovered and Non-recovered).