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Original research

The T1-weighted/T2-weighted ratio as a biomarker of anti-NMDA receptor encephalitis

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ABSTRACT

Background Anti-N-methyl-D-aspartate receptor (NMDAR) encephalitis rarely causes visible lesions in conventional MRI, yet advanced imaging detects extensive white matter damage. To improve prognostic capabilities, we evaluate the T1-weighted/T2-weighted (T1w/T2w) ratio, a measure of white matter integrity computable from clinical MRI sequences, in NMDAR encephalitis and examine its associations with cognitive impairment.

Methods T1-weighted and T2-weighted MRI were acquired cross-sectionally at 3 Tesla in 53 patients with NMDAR encephalitis (81% women, mean age 29 years) and 53 matched healthy controls. Quantitative and voxel-wise group differences in T1w/T2w ratios and associations with clinical and neuropsychological outcomes were assessed. P-values were false discovery rate (FDR) adjusted where multiple tests were conducted.

Results Patients with NMDAR encephalitis had significantly lower T1w/T2w ratios across normal appearing white matter (p=0.009, Hedges' g=−0.51), which was associated with worse verbal episodic memory performance (r=0.39, p=0.005, p(FDR)=0.026). White matter integrity loss was observed in the corticospinal tract, superior longitudinal fascicle, optic radiation and callosal body with medium to large effects (Cohen's d=[0.42–1.17]). In addition, patients showed decreased T1w/T2w ratios in the hippocampus (p=0.002, p(FDR)=0.005, Hedges' g=−0.62), amygdala (p=0.002, p(FDR)=0.005, Hedges' g=−0.63) and thalamus (p=0.010, p(FDR)=0.019, Hedges' g=−0.51).

Conclusions The T1w/T2w ratio detects microstructural changes in grey and white matter of patients with NMDAR encephalitis that correlate with cognitive performance. Computable from conventional clinical MRI sequences, this measure shows promise in bridging the clinico-radiological dissociation in NMDAR encephalitis and could serve as an imaging outcome measure in clinical trials.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Conventional MRI shows no abnormalities in the majority of patients with N-methyl-D-aspartate receptor (NMDAR) encephalitis despite severe clinical disease courses. Advanced imaging studies using functional MRI or diffusion tensor imaging have identified characteristic imaging alteration in NMDAR encephalitis, but require dedicated MRI acquisition and analysis pipelines that are not available in clinical routine settings.

WHAT THIS STUDY ADDS

⇒ The T1-weighted/T2-weighted (T1w/T2w) ratio can be calculated from conventional MRI sequences without additional acquisition time. Patients show significantly reduced T1w/T2w ratios in normal appearing white and deep grey matter structures, including the hippocampus, amygdala and thalamus. White matter T1w/T2w ratio correlated with cognitive performance in patients.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ The T1w/T2w ratio sensitively detects structural brain damage in patients with NMDAR encephalitis that correlates with clinical manifestation. It thus represents a readily available and clinically meaningful MRI measure that can help to overcome the clinico-radiological paradox in NMDAR encephalitis and that could serve as prognostic MRI marker and imaging outcome measure in clinical trials on NMDAR encephalitis.

INTRODUCTION

Anti-N-methyl-D-aspartate receptor encephalitis (NMDAR encephalitis) is a severe autoimmune encephalitis that can manifest with a variety of symptoms including anxiety, psychotic symptoms, dyskinesia, epileptic seizures, autonomic dysregulation and impaired consciousness.[1 2] Despite the availability of effective treatments and good overall functional outcome, many patients suffer from long-term cognitive deficits.[3 4]

Remarkably, less than half of patients with NMDAR encephalitis show abnormalities in routine MRI, such as T2-weighted (T2w)/fluid-attenuated inversion recovery (FLAIR) hyperintense lesions.[5 6] Moreover, in patients with abnormal MRIs, detected lesions are usually small and do not correspond well to clinical symptoms. As a result, the diagnostic value of routine MRI is limited. Regarding the predictive value of MRI lesions on disease outcome, results are heterogeneous. In an analysis of almost 400 patients with detailed

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information on clinical outcome, an abnormal MRI was associated with worse functional status after 1 year,[7] a finding that was later replicated.[8] Likewise, an abnormal MRI at disease onset was associated with poorer functional neurological outcome in children with NMDAR encephalitis.[9] In contrast, a normal MRI does not rule out severe trajectories with poor long-term outcomes and several studies observed no correlation between conventional MRI abnormalities and long-term outcomes.[10–12] However, current analyses of the predictive value of clinical MRI studies are based on dichotomous normal/abnormal MRI evaluations, not taking into account the amount, size and distribution of lesions.

For these reasons, better imaging markers of NMDAR encephalitis are needed to improve prognostic information and to allow guidance of treatment decisions.[13] Advanced imaging techniques such as resting state functional MRI, positron emission tomography and volumetric analyses have shown decreased hippocampal connectivity, reduced density of active NMDARs and reduced hippocampus volumes that are not detectable in conventional imaging studies and that correlate well with clinical symptoms.[14–23] In addition, widespread white matter damage and microstructural changes can be detected using diffusion tensor imaging,[15 24] pointing to the role of oligodendrocyte function in the pathophysiology of NMDAR encephalitis.[25 26] However, these imaging methods require dedicated setups, long acquisition times and refined analysis pipelines that are currently not available in clinical settings.

The T1-weighted (T1w)/T2w ratio is a recently developed method to map myelin content in the brain and thereby detect changes in white matter microstructure. In addition, the T1w/T2w ratio is suited to assess the integrity of deep grey matter structures that contain myelin.[27] Importantly, this measure can be computed from conventional T1w and T2w images that are acquired with clinical routine MRI protocols.[28] Recently, we demonstrated that a standardised T1w/T2w (sT1w/T2w) ratio is highly reliable and reproducible and can be used to detect microstructural changes associated with clinical symptoms in different patient populations.[29–31] The sT1w/T2w ratio therefore seems to be specifically well suited to detect white matter and deep grey matter abnormalities in NMDAR encephalitis based on clinical routine MRI scans.

Here, we investigated the T1w/T2w ratio in a large sample of patients with NMDAR encephalitis in comparison to matched healthy controls. We studied (1) group differences of the T1w/T2w ratio in normal appearing cerebral white matter (NAWM); (2) group differences of the T1w/T2w in deep grey matter structures and (3) assessed associations of T1w/T2w ratio alterations in white and deep grey matter with cognitive deficits in patients using a comprehensive test battery covering all major cognitive domains.

METHODS

Participants

Patients were recruited from Germany as part of an observational study conducted at the Charité - Universitätsmedizin Berlin, Germany. All patients fulfilled the current diagnostic criteria, that is, typical clinical symptoms and detection of anti-NMDA-receptor antibodies in the cerebrospinal fluid.[32] Patients were included if they were at least 18 years old and German native speakers (neuropsychological tests were conducted in German only). All patients were seronegative for antibodies against myelin oligodendrocyte glycoprotein and aquaporin-4. Patients were recruited after the acute disease stage and the first study visit was scheduled as soon as possible. Follow-up visits were scheduled every 2 years. Due to the exploratory study approach, no prior power calculation was performed. Healthy controls were matched to patients by gender and age using R package e1071.[33]

MRI acquisition

MRI acquisition was performed on a 3 Tesla system (Tim Trio, Siemens Medical Systems, Erlangen, Germany) with a 20-channel head coil. The protocol included a three-dimensional (3D) magnetization-prepared rapid acquisition gradient echo (MPRAGE; T1w, repetition time TR=1900 ms, echo time TE=2.55 ms, inversion time TI=900 ms, 1 mm isotropic resolution), a 3D T2 Sampling Perfection with Application optimised Contrast using different flip angle Evolution (T2SPACE; T2w, TR=5000 ms, TE=502 ms, 1 mm isotropic resolution) and a 3D FLAIR (TR=6000 ms, TE=388 ms, TI=2100 ms, 1 mm isotropic resolution) sequence.

MRI analysis

MRI analysis was performed as described previously[30]: T1w and T2w images were bias field corrected via non-parametric non-uniform intensity normalisation.[34] The T1w image was changed to a robust field of view and oriented to Montreal Neurological Institute 152 (MNI) space using the FMRIB Software Library (FSL).[35] Then, the T2w image was co-registered to the corrected T1w image and both were registered to standard MNI space via spline interpolation using FMRIB's Linear Image Registration Tool (FLIRT).[36 37] We used the Computational Anatomy Toolbox V.11.09[38] in SPM12 V.7219 to generate a brain mask and segment tissue into grey matter, white matter and cerebrospinal fluid. Median intensity values from T1w and T2w were extracted for all white matter and all grey matter.

Deep grey matter masks for the hippocampus, the amygdala, the thalamus and the basal ganglia were created from the T1w MPRAGE image using FMRIB's Integrated Registration and Segmentation Tool (FIRST) and all masks were checked visually.

T2w and FLAIR images from the current study were assessed for visible lesions by an experienced researcher and neurologist (CF, 18 years of experience). Lesions were segmented by the lesion growth algorithm (Schmidt *et al*, 2012) as implemented in the Lesion Segmentation Toolbox V.3.0.0 (https://www.applied-statistics.de/lst.html). MRI data of one patient showed severe artefacts in deep grey matter structures and was therefore excluded from analyses of deep grey matter structures.[39] Another patient had substantial global atrophy leading to imprecise white matter segmentation and implausible white matter T1w/T2w values and was therefore excluded from all analyses.

T1w/T2w ratio and T1w/T2w ratio calculation

We calculated the T1w/T2w using FSL stats[40] by dividing the processed 3D T1w image by the spatially registered 3D T2w image. For standardisation, we computed a scaling factor by dividing the median grey matter intensity value in the T1w image by the median grey matter intensity value in the T2w image. A scaled T2w image was obtained by multiplying the T2w image by the scaling factor. The T1w/T2w ratio was then calculated using the equation from Misaki and colleagues[41]:

$$sT1w/T2w\ ratio = \frac{T1w - sT2w}{T1w + sT2w}$$

Finally, we extracted mean T1w/T2w values from all grey matter, NAWM (white matter mask minus lesion mask generated by LST toolbox) and deep grey matter structures for each subject

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using FSL. A fully automated script for T1w/T2w ratio calculation is available online (https://github.com/timhartung/T1T2).

As a post hoc analysis, we identified clusters of voxels where patients and controls differed significantly in white matter T1w/T2w ratio. To improve spatial normalisation, T1w/T2w maps were registered to MNI-152 space using non-linear registration via FMRIB's Non-linear Image Registration Tool (FNIRT). Voxel-wise permutation-based independent samples t-tests were performed using FSL randomisation with threshold-free cluster enhancement, 5000 permutations and a binary white matter mask from the Harvard-Oxford subcortical atlas. To evaluate congruence with functional white matter networks, we visually assessed overlap with the white matter functional atlas provided by Peer and colleagues.[42]

Clinical and neurocognitive measures

The neuropsychological test battery comprised five cognitive domains: (1) executive function (Test of Attentional Performance (TAP) Go/No-go paradigm), (2) working memory (forward digit span test from the Wechsler Adult Intelligence Scale IV), (3) verbal episodic memory (Rey Auditory Verbal Learning Test), (4) visual episodic memory (Rey–Osterrieth Complex Figure) and (5) attention (TAP tonic alertness).

The modified Rankin Scale (mRS) was used to assess neurological disability on a scale from 0 (no symptoms) to 5 (full-time nursing required) at disease maximum and at the time of study MRI.

Statistical procedures

All quantitative statistical analyses were performed in R V.4.0.2,[43] all tests were two-tailed and $p<0.05$ was considered statistically significant.

Group comparisons

Since visual inspection of histograms and Shapiro-Wilk tests indicated normal distribution for T1w/T2w ratios for all brain structures in both groups, we used Welch's t-tests to assess group differences of the T1w/T2w ratio in NAWM between patients with NMDAR encephalitis and healthy controls. Effect sizes were calculated as Hedges' g.

To estimate the T1w/T2w ratio's ability to distinguish between patients and healthy individuals, receiver operating characteristics (ROC) curves were plotted for each region of interest, as well as for an unweighted and weighted combined measure using the pROC package.[44 45] The weighting was based on the ORs derived from a multivariable logistic regression model. CIs for the ROC curve and area under the curve (AUC) were estimated with a bootstrapping method using the pROC package.[44]

Association with cognitive and clinical measures

The association of T1w/T2w ratio with the peak mRS and the mRS on the date of the study MRI was computed as Kendall's τ correlation. All other associations between the T1w/T2w ratio in NAWM/deep grey matter structures and socio-demographic, clinical and neuropsychological measures were assessed with product-moment correlations.

Multiple testing

P values of voxel-wise permutation-based hypothesis tests were corrected for family-wise error (FWE) rate in FSL randomise. Correlations between white matter T1w/T2w ratio and cognitive deficits were corrected for false discovery rate (FDR) across the five cognitive domains.

Table 1 Patient sample characteristics (n=53). *Abbreviations*: IQR interquartile range, mRS modified Rankin Scale, FLAIR fluid-attenuated inversion recovery.

Characteristic	n (%)*
Socio-demographic characteristics	
Age (years), median (IQR)	26 (23–36)
Sex	
Female	43/53 (81)
Male	10/53 (19)
Education (years)	13.5 (2.5)
Clinical characteristics	
Time since onset (years), median (IQR)	3.5 (1.8–5.2)
Peak mRS	
2	5/53 (9)
3	12/53 (23)
4	15/53 (28)
5	21/53 (40)
mRS at study MRI	
0	14/53 (26)
1	20/53 (38)
2	17/53 (32)
3	1/53 (2)
4	1/53 (2)
Acute stage symptoms	
Psychiatric	49/53 (92)
Seizures	37/53 (70)
Movement	28/53 (53)
Autonomic	18/53 (34)
Cognitive	48/53 (91)
Relapse	
No relapse	32/53 (60)
Relapse before study MRI	18/53 (34)
Relapse after study MRI	3/53 (6)
Second line therapy	28/53 (53)
Acute stage MRI abnormal	24/53 (45)
Study MRI T2-weighted/FLAIR abnormal	15/53 (28)

*Unless otherwise indicated; mRS, modified Rankin Scale.

Exploratory analyses for deep grey matter structures were FDR-corrected for six group comparisons (hippocampus, amygdala, thalamus, caudate, putamen and pallidum) as well as 15 correlations with cognitive scores (associations between five cognitive domains and each of the three structures with significant group differences).

Missing values

Missing values in socio-demographic, clinical and neuropsychological variables (table 1) were excluded in a pairwise manner from correlation analyses.

RESULTS

Participants

Patients with NMDAR encephalitis (n=53) were mostly women (81%), median age (IQR) was 26 (23–36) years and median time since onset (IQR) was 3.5 (1.8−5.2) years (table 1). Most patients were severely impaired during the acute phase (median mRS=4), but had substantially improved at the time of study MRI (median mRS=1). At the acute disease stage, 45% (24/53) of patients had visible pathology in brain MRI, and 28% (15/53) had visible pathology in the T2w/FLAIR in our study MRI.

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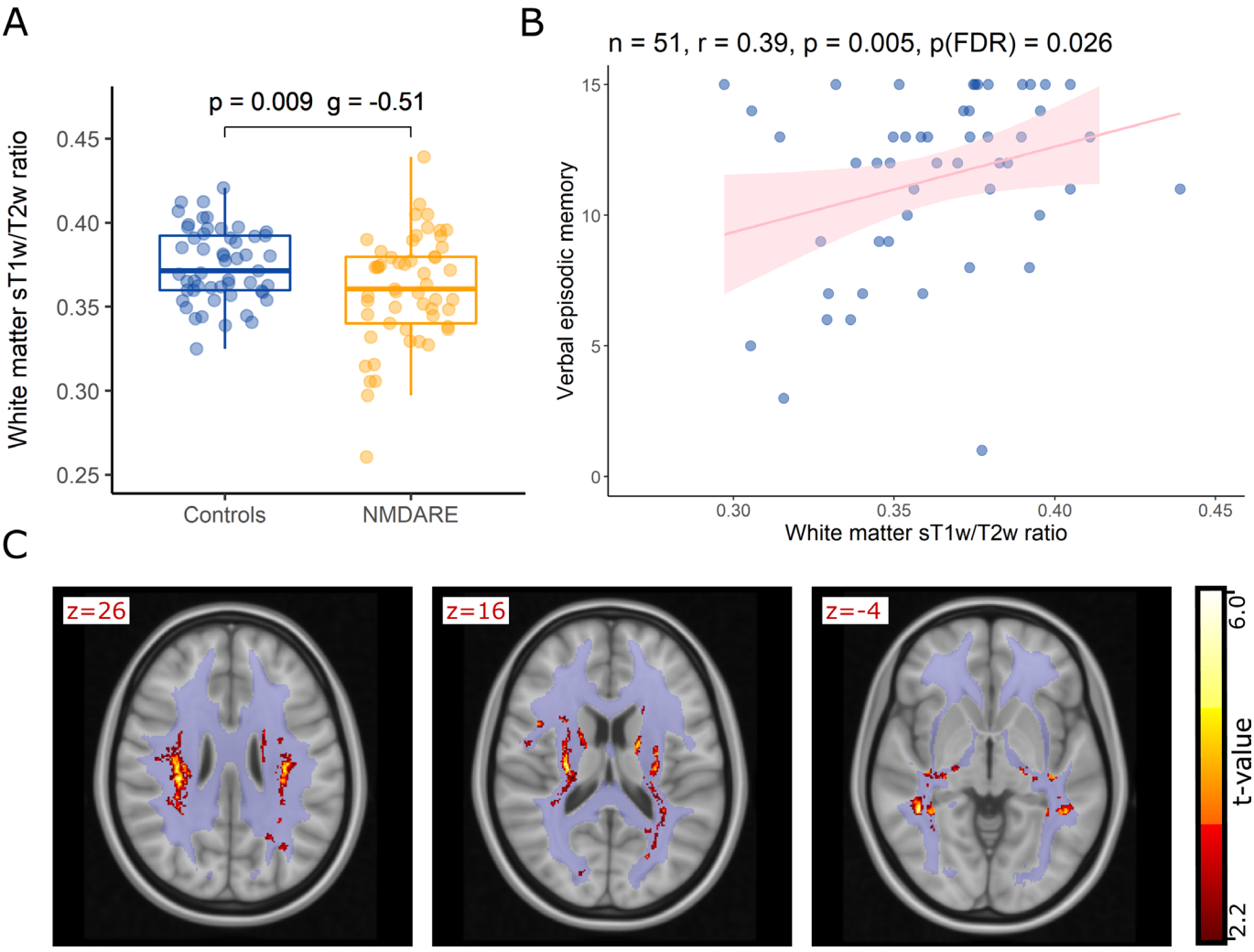

Figure 1 (A) Mean standardized T1-weighted/T2-weighted (sT1w/T2w) ratio in healthy control participants and patients with N-methyl-D-aspartate receptor encephalitis (NMDARE) across all normal appearing cerebral white matter voxels. P-value according to independent samples t-test, effect size as Hedges' g. (B) Association between verbal episodic memory (auditory verbal learning test delayed recall) and normal appearing white matter sT1w/T2w ratio. (C) Significant (p[family-wise error rate corrected] <0.05) voxel-wise group differences (red/orange) in white matter (blue) sT1w/T2w ratio. Z-coordinates according to Montreal Neurological Institute-152 space. p(FDR) false detection rate adjusted p-value.

Details on conventional MRI abnormalities in the acute stage and our study MRI are provided in the online supplemental eTable 4. As previously reported in more detail, all patients showed cognitive deficits and about half the patients showed severe cognitive impairment.[4] Healthy control participants were well matched for gender (χ^2=0.22, p=0.637) and age (t=0.27, p=0.785).

White matter

Patients had a significantly lower T1w/T2w ratio in NAWM compared with matched healthy control participants (p=0.009, Hedges' g=−0.51) (figure 1A). Permutation-based voxel-wise tests showed six white matter clusters >100 voxels where patients with NMDAR encephalitis had significantly lower T1w/T2w ratios than healthy control participants (p(FWE)<0.05). These affected the corticospinal tract, superior longitudinal fascicle, anterior thalamic radiation, optic radiation, callosal body and periventricular areas around posterior horns of the lateral ventricles (figure 1C) with effect sizes ranging from medium to large (t=(2.2–6.0), Cohen's d=(0.42–1.17)). Regarding functional white matter networks, alterations mostly affected the superior longitudinal fasciculus system with small parts extending to the inferior longitudinal fasciculus system, inferior corticospinal tract system and dorsal frontoparietal tract system.

Importantly, NAWM T1w/T2w ratio correlated significantly with verbal episodic memory in patients (r=0.39, p=0.005, p(FDR)=0.026; figure 1B). Performance in other cognitive domains was not associated with NAWM T1w/T2w ratio (online supplemental eTable 1).

Deep grey matter structures

The T1w/T2w ratio was significantly reduced in patients compared with controls in the hippocampus (p=0.002, p(FDR)=0.005, Hedges' g=−0.62), amygdala (p=0.002, p(FDR)=0.005, Hedges' g=−0.63) and thalamus (p=0.010, p(FDR)=0.019, Hedges' g=−0.51) (figure 2). There were no significant group differences in the T1w/T2w ratio of the basal ganglia (figure 2).

A significant association between T1w/T2w ratio in the thalamus and working memory (forward digit span) did not survive FDR-correction for multiple testing (r=−0.37, p=0.007, p(FDR)=0.100). There were no other significant correlations between neuropsychological test scores and the T1w/T2w ratio

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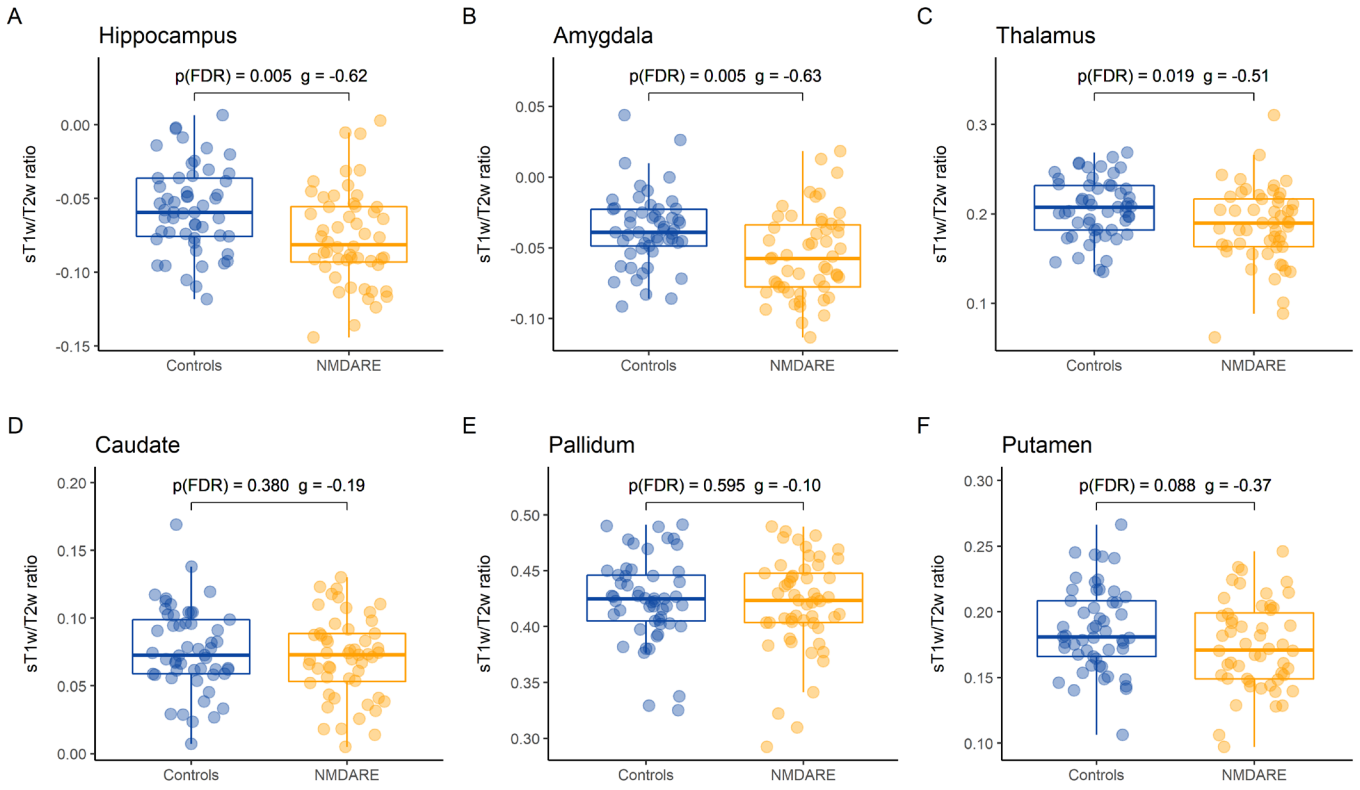

Figure 2 Standardised T1-weighted/T2-weighted (sT1w/T2w) ratio in patients with N-methyl-D-aspartate receptor encephalitis (NMDARE) and controls for deep grey matter structures; p(FDR) according to independent samples t-test corrected for false discovery rate (FDR), effect size as Hedges' g.

in deep grey matter structures with significant group differences (online supplemental eTable 2).

Sensitivity analyses

ROC analyses showed significantly above-chance ability to distinguish between patients and controls for structures with significant group differences (AUC (95% CI): NAWM 0.64 (0.52 to 0.75), hippocampus 0.69 (0.59 to 0.79), amygdala 0.70 (0.59 to 0.79), thalamus 0.64 (0.53 to 0.75), combined unweighted 0.70 (0.60 to 0.80), combined weighted 0.64 (0.53 to 0.74); online supplemental eFigure 1).

Age was significantly negatively associated with T1w/T2w ratio in white matter and deep grey matter structures (product-moment correlation r range −0.4 to −0.29, p range 0.003 to 0.038) except putamen (r=0.07, p=0.621) and pallidum (r=−0.19, p=0.163; online supplemental eFigure 2), but was not significantly associated with cognitive test scores in patients with NMDAR encephalitis (absolute product-moment correlation r range 0.00 to 0.27, all p>0.05). There was no significant gender difference in the NAWM T1w/T2w ratio of patients with NMDAR encephalitis (p=0.223, g=0.45).

There was no significant association between the T1w/T2w ratio and peak mRS (Kendall's τ range 0.07 to 0.20, all p>0.15), mRS at time of study MRI (τ range 0.05 to 0.11, all p>0.41) or time since disease onset (product-moment correlation r range −0.04 to −0.19, all p>0.90). Patients did not differ significantly in T1w/T2w ratio based on acute phase clinical symptoms (all p(FDR)>0.05, online supplemental eTable 3). There was no difference in T1w/T2w ratio between patients who received/did not receive second line treatment (Hedges' g (95% CI)=0.46 (–0.08 to 1.01), p=0.141), or between patients with/without relapse before the study MRI (Hedges' g (95% CI)=−0.17 (−0.73 to 0.40), p=0.622).

DISCUSSION

We studied the T1w/T2w ratio as a clinically available MRI marker of white matter damage in 53 patients with NMDAR encephalitis and 53 matched control participants. We observed significantly lower T1w/T2w ratio for NAWM in patients compared with matched controls, consistent with reduced white matter integrity. Within white matter, six clusters across all major central tracts were particularly affected. Importantly, the T1w/T2w ratio in NAWM was significantly associated with verbal episodic memory in patients. Furthermore, patients had reduced T1w/T2w ratios in the hippocampus, amygdala and thalamus indicating microstructural damage of deep grey matter structures. These findings highlight the clinical applicability of the T1w/T2w ratio as a marker of reduced white matter integrity in patients with NMDAR encephalitis.

Reduction of the T1w/T2w ratio was widespread and affected several central fibre tracts. Interestingly, these changes were not detectable by visual inspection of the clinical images from which the T1w/T1w ratio was derived. ROC analyses indicated that the T1w/T2w ratio in NAWM has the ability to distinguish between patients and controls and may thus add important diagnostic information beyond visual inspection of the images. Importantly, NAWM T1w/T2w ratio correlated significantly with verbal episodic memory in patients. This is in line with previous studies that identified widespread alterations of deep and superficial white matter using diffusion tensor imaging, which was also associated with impairments in verbal episodic memory.[16 24]

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These findings suggest that persistent white matter damage is a neural correlate of long-term cognitive impairment in patients with NMDAR encephalitis. Earlier models of NMDAR encephalitis did not account for white matter damage, as antibody binding to neuronal NMDARs leads to receptor internalisation and consequently to functional changes without substantial neuronal damage.[46] However, recent experimental studies have demonstrated the importance of not just neuronal but also oligodendrocyte NMDAR signalling. Indeed, impaired oligodendrocyte NMDAR function may have a detrimental effect on myelination and remyelination.[25 26] Thus, there is a plausible mechanism by which anti-NMDAR antibodies can lead not just to functional but also microstructural changes.

The pattern of white matter damage may bear important implications for functional and cognitive outcomes. The superior longitudinal fascicle (SLF) was the most affected white matter tract in our study. The observed correlation with deficits in verbal episodic memory is thus highly plausible, considering the crucial role of this structure for language processing.[47] Moreover, the major SLF component terminates in the dorsolateral prefrontal cortex, a brain region central to working memory that also promotes long-term memory formation.[48] Recent studies have demonstrated that cerebral white matter can also be analysed from a network perspective, both as a structural network[49] and as a functional connectivity network.[42] To estimate the functional implications of the observed white matter changes, we visually assessed overlap with the white matter functional atlas developed by Peer and colleagues.[42] Here, we found—in agreement with our tract-based analysis—that changes mostly mapped to the superior longitudinal fasciculus system. Colato *et al* recently identified grey and white matter networks of microstructural damage assessed using the sT1w/T2w ratio in patients with multiple sclerosis.[49] Interestingly, they also identified an independent component (WM-IC6) that closely matches the damage pattern in our patients with NMDAR encephalitis. This could potentially indicate that this white matter network covers a specifically vulnerable brain region, or a brain region where multiple sclerosis and NMDAR encephalitis share (downstream) pathophysiological mechanisms.

In addition, we observed significant reductions in the T1w/T2w ratio of deep grey matter structures in patients when compared with controls. Evidence of hippocampal damage is consistent with previous volumetric and diffusion tensor studies in patients with NMDAR encephalitis.[15 16 20 50] The hippocampus is recognised to be particularly vulnerable to anti-NMDAR antibodies, as it possesses the highest density of NMDA receptors within the brain.

Interestingly, we also observed a reduced T1w/T2w ratio in the amygdala and thalamus. While there are some reports on functional changes in the amygdala[20] and thalamic volume reductions in patients with paediatric NMDAR encephalitis,[9] there are few, if any, published imaging findings on microstructural changes in these two structures. However, a recent neuropathological study found pronounced inflammation in both the thalamus and the amygdala.[51] It is at least plausible that functional and microstructural changes in the amygdala are underlying some of the common psychiatric symptoms of NMDAR encephalitis such as mood change or anxiety.

Clinical implications

Our analyses show that the T1/T2w ratio provides information beyond visible lesions from clinical scans and thus provides important additional diagnostic information, especially since routine MRI is unremarkable in the majority of patients. The consistency of our findings with previous results from diffusion tensor imaging, volumetry and neuropathological studies suggests a high validity of this method for identifying brain changes that occur in NMDAR encephalitis. Furthermore, the NAWM T1w/T2w ratio was associated with verbal episodic memory, suggesting potential use as a prognostic marker of long-term cognitive deficits.

Our analyses demonstrate that the T1w/T2w ratio is an easily applicable MRI measure that can sensitively detect microstructural damage in patients with autoimmune encephalitis. Importantly, this measure is based on existing sequences that are part of most standard protocols. It can be readily applied to clinical settings without adding additional MRI sequences to the scan and therefore without increasing acquisition time. However, calculation of values requires installation of freely available standard software. To facilitate use of the T1w/T2w ratio in future studies, we provide a guide for the required software tools and a fully automated analysis script online (https://github.com/timhartung/T1T2). If future studies further corroborate the clinical usefulness of T1w/T2w analyses, such analysis scripts can be directly implemented in MRI scanner software allowing for automated calculation of T1w/T2w values.

Implications for future research

Longitudinal studies with assessments during the acute stage and follow-up visits should be conducted to validate this method, further assess its prognostic value and assess white matter changes during clinical remission. Larger studies in representative samples could seek to identify optimal cut-off points for T1w/T2w values in particular brain regions and/or age groups. Future studies could also directly compare the observed changes to other patient groups such as other autoimmune and/or viral encephalitides and further inflammatory brain diseases including multiple sclerosis.

In addition, this method should be cross-validated and directly compared with other imaging methods which may be more sensitive to specific pathological changes such as methods of quantitative MRI.[52]

Strengths and limitations

Strengths of our study include the relatively large sample size enabling adequately powered analyses, the extensive and standardised neuropsychological test battery allowing for a precise characterisation of cognitive deficits across all domains, the representative age-distribution and gender-distribution of our sample ensuring generalisability of our results and the well-matched control group.

A limitation of this study is that the scaling method does not enable detection of disease specific changes in cortical grey matter, although grey matter is likely to be affected to a similar extent as white matter.[5] Because the scaling factor is based on the intensity of cortical grey matter, signal from these areas is zeroed. In addition, grey matter pathology may affect the scaling factor and thereby alter the standardised T1w/T2w ratio in other brain regions as well. Future studies could address this by comparing this method to other scaling methods, for example, based on cerebrospinal fluid.

CONCLUSION

The T1w/T2w ratio is sensitive to white matter damage in NMDAR encephalitis and can be easily and quickly computed from MRI sequences already used in typical clinical scans.

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Without requiring additional scanning time, this measure helps to distinguish patients with NMDAR encephalitis from healthy subjects and correlates with cognitive deficits. The T1w/T2w can therefore serve as a biomarker of NMDAR encephalitis that adds valuable information to complement visual assessment of clinical MRI scans.

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