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Patient-Reported Outcome Measures in NMDA Receptor Encephalitis

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Abstract

Background and Objectives

The characteristics of persistent long-term symptoms and their contribution to subjective quality of life remain unclear in patients with NMDAR encephalitis. In this study, we aimed to evaluate postacute neuropsychiatric symptoms, subjective cognitive complaints, and disease coping mechanisms and identify predictors of health-related quality of life (HRQoL) after N-methyl-D-aspartate receptor (NMDAR) encephalitis.

Methods

This cross-sectional observational study investigated patients with NMDAR encephalitis in the postacute phase. Psychometric scales included assessment of neuropsychiatric symptoms (i.e., fatigue, sleep, anxiety, and depressive symptoms), HRQoL, everyday independence, metamemory (i.e., self-rated ability, satisfaction, and use of strategies), and coping strategies (i.e., self-efficacy, disease-related coping, and stress management).

Results

A total of 50 patients (mean age 26.0 ± 10.1 years, 86% female) participated at a median of 4.15 (range 0.3–30.3) years after symptom onset. Patients reported significantly increased levels of anxiety (Beck Anxiety Inventory: 10.5 ± 7.7 [mean ± SD], 95% CI [8.32–12.71], $p < 0.001$) and depressive (Beck Depression Inventory–II: 11.4 ± 7.7 [9.22–13.62], $p = 0.001$) symptoms compared with the normative population. Both sleep problems (Pittsburgh Sleep Quality Index: 5.8 ± 3.0 [4.98–6.66], $p < 0.001$) and motor and cognitive fatigue (Fatigue Scale for Motor and Cognitive Function: 50.5 ± 23.1 [42.5–58.4], $p < 0.001$) were significantly more prevalent. Moreover, lower self-rated memory ability (Multifactorial Memory Questionnaire score: 54.6 ± 8.5 [52.1–57.1], $p = 0.004$) was associated with greater reliance on compensatory strategies and memory aids ($r = -0.41$, $p = 0.004$). Patients used significantly fewer cognitive coping strategies, such as relativization (11.7 ± 4.7 [10.3–13.1], $p = 0.001$), while depressive coping prevailed (49.1 ± 15.5 [44.5–53.8], $p < 0.001$). It is important to note that HRQoL was predicted by self-reported affective symptoms, self-efficacy, and coping behaviors in multivariable regression analyses, but not by acute disease severity or postacute physical disability.

Discussion

Our findings show that persistent neuropsychiatric and subjective cognitive concerns explain a large part of the reduced quality of life in patients with NMDAR encephalitis. These findings have important implications for a patient-centered postacute care and the role of disease coping strategies in the neurorehabilitation of autoimmune encephalitis.

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Glossary

BDI = Beck Depression Inventory; **FKK** = Competence and Control Beliefs Questionnaire; **FKV** = Freiburg Questionnaire of Coping with Illness; **FSMC** = Fatigue Scale for Motor and Cognitive Function; **HRQoL** = health-related quality of life; **ICU** = intensive care unit; **IQR** = interquartile range; **MMQ** = Multifactorial Memory Questionnaire; **mRS** = modified Rankin Scale; **NMDAR encephalitis** = N-methyl-D-aspartate receptor encephalitis; **PROM** = patient-reported outcome measure; **PSQI** = Pittsburgh Sleep Quality Index; **SVF78** = Stress Coping Style Questionnaire.

Introduction

N-methyl-D-aspartate receptor (NMDAR) encephalitis is a severe and life-altering neurologic disease. The remission of acute symptoms including altered levels of consciousness, seizures, language impairment, amnesia, or psychosis with immunotherapy indicates a significant potential for recovery. Although clinical scales suggest generally favorable outcomes,[1] they frequently lack sensitivity and specificity for the diverse and multifaceted postacute experiences.[2,3] It is, therefore, necessary to develop a more targeted evaluation of postacute symptoms.[4-6] In this study, we present a comprehensive cross-sectional assessment of quality of life, neuropsychiatric symptoms, metacognitive outcomes, and disease coping behaviors.

Recent studies have started to characterize postacute symptoms and adaptive behaviors in patients with autoimmune encephalitis.[2,5,7,8] Frequent residual symptoms include sleep disorders,[7,9-13] fatigue,[2,10] mood alterations,[2,7,14-16] and persistent cognitive complaints.[7,14-17] These cognitive complaints have also been observed in neuropsychological follow-up assessments and shown to persist in most patients even 5 years after onset, especially in the domains working memory, verbal memory, and executive functions.[15-18] In a study of 61 patients recovering from NMDAR encephalitis, most patients experienced compromised psychosocial functioning after the acute phase.[19] Commonly reported problems included being worried about the future, feeling isolated, and health problems interfering with day-to-day life. In addition, patients may struggle with memory gaps for acute disease stage, psychiatric stigma,[20] lifestyle disruptions,[20] returning to previous work or school activities,[19] and an uncertain long-term prognosis.[19,20]

Although behavioral alterations and affective symptoms may persist for several years and affect both quality of life and rehabilitation outcomes,[7,21] only a third of the patients with NMDAR encephalitis reported receiving neuropsychiatric long-term care.[7] In addition, previous studies largely describe mixed samples of patients with different antibodies, rely on self-reported diagnoses, or provide clinician-assessed accounts of postacute symptoms. To understand the complex needs and identify the most relevant treatment options for patients recovering from NMDAR encephalitis, it is essential to determine the frequency and characteristics of these long-term symptoms.

This study, therefore, aims to (1) identify self-reported long-term symptoms and their disease burden in 50 patients with NMDAR encephalitis; (2) provide a detailed description of mood, fatigue, and sleep outcomes; (3) determine how postacute memory worries relate to objective memory performance; (4) examine disease coping strategies; and (5) establish predictors of health-related quality of life (HRQoL) in patients with NMDAR encephalitis.

Methods

Participants

In this cross-sectional observational study, we recruited 50 patients from the Department of Neurology at Charité—Universitätsmedizin Berlin (Germany) between 2017 and 2020. All patients fulfilled the current diagnostic criteria for NMDA receptor encephalitis.[22] Patients were diagnosed at university hospitals across Germany and were invited to participate in this study without any clinical selection criteria. We enrolled all available patients at all stages of the postacute phase (median 4.15 years, range 0.3–30.3, interquartile ranges (IQRs) = 1.76–6.27 years after the acute phase). The final sample was representative of larger cohort studies regarding age (mean 26.0 ± 10.1 years) and sex distribution (43/50 women [86%], 7/50 men [14%]). Patients filled out printed questionnaires after an on-site study visit and returned the pseudonymized copies by mail. Each patient-reported outcome measure (PROM) was administered once to each patient.

Questionnaires and Scales

Quality of Life and Symptom Scales

We assessed overall self-reported disease outcomes using the scales for HRQoL that comprise a physical, social, and cognitive-emotional subscale. In addition, patients were asked to list their current postacute symptoms and rate the experienced burden on quality of life (scoring 0–100, low to high burden) using an in-house survey (provided along with the PROMs at the study visit). Moreover, we evaluated anxiety and depressive symptoms (Beck Anxiety Inventory and Beck Depression Inventory [BDI-II]), sleep problems (Pittsburgh Sleep Quality Index [PSQI]), and fatigue (Fatigue Scale for Motor and Cognitive Function). Day-to-day independency was assessed using a 10-point in-house scale of activities of daily living (work/education, household, social life, finances, health, travel, nutrition, leisure activities, participation in public life, time management). Each item was scored 1 point for fully regained independence and 0.5 points for relative independence with occasional caregiver assistance. A score of 0 was given if

a patient was fully dependent on their caregiver in the respective domain (total score 0–10, low to high independency).

Metacognitive Scales

Because memory impairment is one of the most frequent postacute sequelae of NMDAR encephalitis,[16] we included the Multifactorial Memory Questionnaire (MMQ) for subjective appraisal of everyday memory function.[23] The 3 individual MMQ subscales assess the satisfaction with one's own memory, self-rated memory ability, and the use of memory strategies and aids in everyday life. Moreover, we collected working memory scores (backward digit span, WAIS-IV) and tested short-term and long-term episodic memory using a list-learning paradigm as their objective counterparts (Rey Auditory Verbal Learning Test).

Disease Coping Scales

To investigate adaptive health behaviors, we collected data on self-efficacy (Competence and Control Beliefs Questionnaire, FKK), the use of stress management styles (Stress Coping Style Questionnaire, SVF78), and disease-related coping strategies (Freiburg Questionnaire of Coping with Illness, FKV), including problem analysis, therapy compliance, and depressive coping tendencies. Patients were instructed to give their own personal assessments and answer the scales at their own pace. Missing data points, if present, were handled according to the recommendations given in the respective manual.

Detailed information about the normative populations for all scales is provided in eTables 1–2.

Statistical Analysis

Descriptive statistics are provided as mean (±SD or median [range and IQRs]). We compared questionnaire scores with the respective normative data using one-sample *t* tests with Cohen d as effect size.

Pearson and Spearman correlations were used to investigate the association of self-reported outcomes with clinical data. Multiple comparison correction was performed using Benjamini-Hochberg FDR correction.

We analyzed predictors of postacute HRQoL using 3 multivariable linear regression models. *Model 1* included scales of self-reported outcomes, i.e., anxiety, depressive symptoms, sleep problems, perceived symptom burden, and independence. We used mean imputation for symptom burden, given missing data points (6%). We also conducted a simple regression analysis using fatigue as a predictor variable for postacute HRQoL. This approach was pursued, given missing fatigue scale data in 30% of the patients, which could have adversely affected the validity of the linear multiple regression model.

Model 2 included adaptive behavioral scales, i.e., self-efficacy and stress management strategies.

Model 3 investigated the effects of disease severity during the acute phase, i.e., the length of hospitalization, intensive care unit (ICU) admission, highest experienced disease severity with the modified Rankin Scale (mRS), and treatment delay. In this study, we used median or mean imputation for continuous variables, with the choice between the 2 methods based on the skewness of the data. Similarly, for categorical variables, mode imputation was applied. This approach was necessary because of missing data points in both continuous and categorical variables (ranging from 2% to 4%). Furthermore, to accommodate the substantial differences in range among continuous variables, we also applied a MinMax Scaler.

Furthermore, we evaluated the potential impact of medication (i.e., antipsychotics or anticonvulsants at the time of study visit) and disease-related life events (i.e., occurrence of relapses and presence of other diseases) on HRQoL using simple regression analyses.

For all regression models, we conducted several steps of quality control, which included testing for independence between predictor variables, linearity between predictor and dependent variables, checking the distribution of residuals, assessing the variance of the residuals, and examining for multicollinearity.

Our data include patients with a wide range of time since disease onset (i.e., 0.3–30.3 years), which comes with the potential caveat of mixing patients with different recovery stages. To address this, we stratified the patients into 3 different time epochs based on the time since disease onset and performed additional explorative analyses on patient-reported outcomes (eMethods 1 and 2, eFigures 1 and 2, eTables 3–6). Note that in the absence of a standard definition within the field, we defined "long-term" as a follow-up period of more than 2 years after symptom onset.

All data were analyzed using R 3.6.1, the package corrplot, and Python (3.10.10) (eMethods 3).

Data Availability

Anonymized data not published within this article will be made available by request from any qualified investigator.

Standard Protocol Approvals, Registrations, and Patient Consents

Informed written consent was obtained from all participants. This study was approved by the Ethics Committee of Charité—Universitätsmedizin Berlin.

Results

Patient Characteristics

The acute disease was characterized by neurologic and psychiatric symptoms, including psychosis, seizures, memory dysfunction, behavioral changes, language/speech dysfunction, and autonomic instability. Most of the patients experienced severe physical disability during the acute disease phase

as indicated by a median maximal mRS score of 5 (range 1–5; IQR 3–5). Most patients (98%; 48/49) received first-line therapy, and 73.5% (36/49) received second-line therapy. The overall cumulative length of hospital stay was 53 (range 10–405; IQR 37.25–88) days. 49% (24/49) of patients were admitted to the ICU with a median stay of 27 (range 1–240; IQR 11–58) days. At the time of the study visit, 2% (1/50) received antipsychotic and 10% (5/50) received anticonvulsive medication, 16% (8/50) of the patients experienced at least one relapse, and 32% (15/46) had additional clinical diagnoses such as depression or Hashimoto thyroiditis. Note that the number of patients included in analyses may vary because of missing data. Denominators inform about the number of available data sets.

We assessed patient-reported outcomes at a median of 4.15 (range 0.3–30.3; IQR 1.76–6.27) years after symptom onset. At the time of the survey, the physical disability outcome was favorable (median mRS score: 1, range 0–3; IRQ 0–1). Around 52% (25/48) of patients had returned to full-time work or education, 13% (6/48) resumed part-time work, and 35% (17/48) were currently not working. Of the latter, 14% (7/49) were on sick leave, 10% (5/49) were retired, and for 8% (4/49), reintegration into work or education was planned.

Independency in day-to-day life was high in most patients, with (regained) independence in a median of 9.5 (range 1.5–10) of 10 examined life domains across patients. We observed the highest levels of independency for the domains of time planning (mean 0.95 ± 0.1), social life (mean 0.90 ± 0.2), and participation in public life (mean 0.90 ± 0.2). The highest need for caregiver assistance, i.e., lowest levels of independency, was reported in the household (mean 0.8 ± 0.3) and work (mean 0.76 ± 0.3) items.

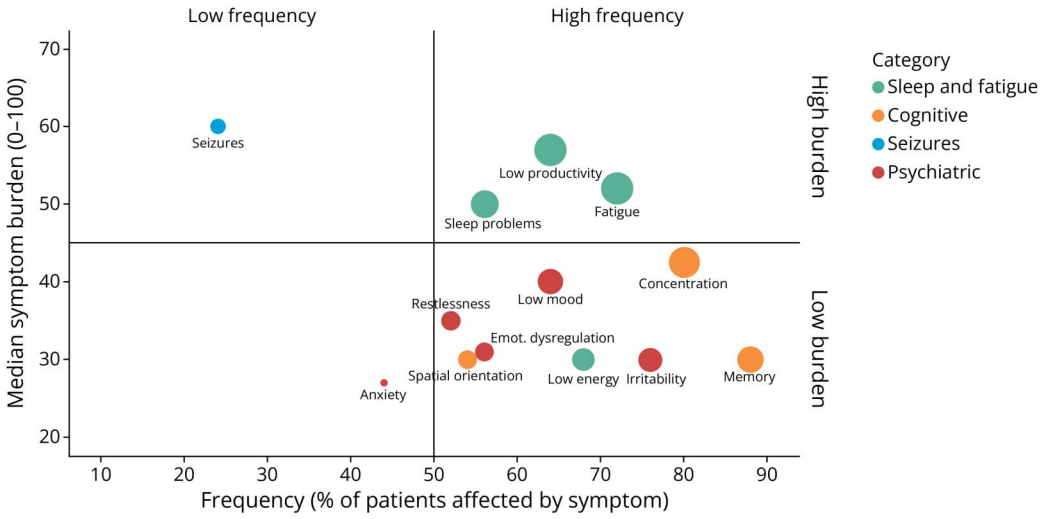
Postacute Complaints and Health-Related Quality of Life

We next examined postacute complaints spontaneously reported by patients (Figure 1). Patients listed a median of 8 complaints (range 0–13; IQR 6–11.75) with a median symptom burden of 41 (range 6–97; IQR 20.33–60.63). Frequent self-reported complaints during the postacute phase of NMDAR encephalitis were memory problems, difficulties with concentration and emotion regulation (including irritability and low mood), and higher fatigability. Notably, seizures caused the highest burden on day-to-day life regardless but occurred less frequently in comparison with other postacute complaints (frequency 24%, median burden 60/100). Structured assessment of HRQoL revealed significantly reduced physical, social, cognitive-emotional, and overall quality of life after NMDAR encephalitis (t [49] = -11.39, $p < 0.001$; Table). HRQoL was reduced across all recovery phases as detailed in our additional exploratory analyses (eMethods 1 for a more detailed discussion of all scales). Correlations with self-reported measures are presented in Figure 2. The list of variables mentioned in the figure, along with the corresponding questionnaires used, can be found detailed in the online supplement (eTable 7).

Mood, Sleep, and Fatigue Scales

Compared with the normative populations, we observed significantly higher rates of depressive and anxiety symptoms in the postacute phase of NMDAR encephalitis (Table).

Figure 1 Self-Reported complaints and Their Perceived Burden on Day-to-Day Life During the Postacute Phase of NMDAR Encephalitis



Point size is scaled by severity (frequency * median symptom burden). Cognitive complaints (apricot/orange) are the most frequently mentioned symptoms. While most psychiatric symptoms (red) and all problems with sleep and fatigue (green) are reported by more than 50% of the patients, most problems with sleep and fatigue also have a high symptom burden (median ≥50). Note that seizures were perceived to have the highest burden on day-to-day life (median 60) despite a relatively low prevalence after the acute phase. Single patients reported compulsive behavior, mania, headache, loss of appetite, and increased dreaming (each N = 1, not shown).

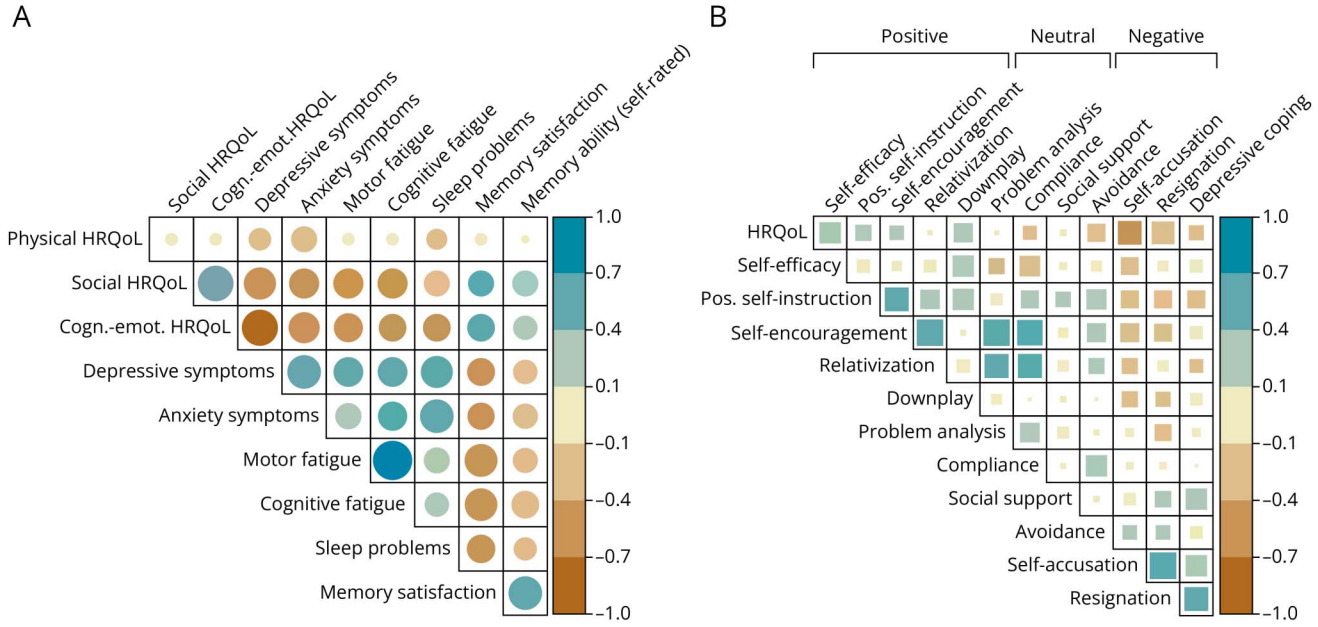
Table Patient-Reported Outcome Measures in Patients With NMDAR Encephalitis

Outcome	Mean	SD	95% CI	Test statistic	*p* Value	d
Health-related quality of life (SEL)	3.03	±0.48	2.89–3.16	*t* (49) = −11.39	<0.001[a]	−1.61
Physical	2.82	±0.84	2.58–3.06	*t* (49) = −11.54	<0.001[a]	−1.63
Social	3.23	±0.58	3.07–3.40	*t* (49) = −8.16	<0.001[a]	−1.15
Cognitive-emotional	3.14	±0.60	2.97–3.32	*t* (49) = −4.64	<0.001[a]	−0.66
Depressive symptoms (BDI-II)	11.42	±7.73	9.22–13.62	*t* (49) = 3.41	0.001[a]	0.48
Anxiety symptoms (BAI)	10.52	±7.72	8.32–12.71	*t* (49) = 7.37	<0.001[a]	1.04
Sleep quality (PSQI)	5.82	±2.96	4.98–6.66	*t* (49) = 4.25	<0.001[a]	0.60
Fatigue (FSMC, total)	50.46	±23.10	42.52–58.39	*t* (34) = 5.06	<0.001[a]	0.86
Cognitive fatigue	24.89	±11.49	20.94–28.83	*t* (34) = 4.83	<0.001[a]	0.82
Motor fatigue	25.57	±12.00	21.45–29.69	*t* (34) = 4.62	<0.001[a]	0.78
Metamemory (MMQ)						
Memory satisfaction	49.12	±15.19	44.80–53.44	*t* (49) = −2.39	<0.02[a]	−0.42
Self-rated memory ability	54.57	±8.48	52.14–57.01	*t* (48) = −3.01	0.004[a]	−0.37
Use of memory strategies	31.20	±10.23	28.29–34.11	*t* (49) = 3.60	0.001[a]	0.52
Internal strategies	12.90	±6.57	11.03–14.77	*t* (49) = 2.78	0.008[a]	0.42
External strategies	18.30	±4.97	16.89–19.71	*t* (49) = 3.74	0.001[a]	0.51
Self-efficacy (FKK)						
Total	62.68	±9.94	59.86–65.50	*t* (49) = −1.08	0.29	−0.15
Self-concept of own abilities	30.78	±7.98	28.51–33.05	*t* (49) = −0.99	0.33	−0.14
Internal locus of control	31.90	±4.68	30.57–33.23	*t* (49) = −0.76	0.45	−0.11
Stress coping (SVF)						
Downplay (+)	9.96	±5.24	8.47–11.45	*t* (49) = 0.65	0.52	0.1
Positive self-instruction (+)	17.90	±4.43	16.64–19.16	*t* (49) = 2.44	0.02[a]	0.35
Avoidance (±)	12.74	±5.31	11.23–14.25	*t* (49) = 1.02	0.31	0.14
Seeking social support (±)	14.96	±6.18	13.20–16.72	*t* (49) = 2.37	0.02[a]	0.38
Resignation (−)	7.18	±4.78	5.82–8.54	*t* (49) = −1.27	0.21	−0.19
Self-accusation (−)	10.49	6.66	8.60–12.38	*t* (49) = −0.16	0.87	−0.03
Disease coping (FKV)						
Problem analysis	35.96	±8.86	33.32–38.59	*t* (45) = −2.44	0.02[a]	−0.36
Relativization	11.69	±4.65	10.29–13.08	*t* (44) = −3.54	0.001[a]	−0.53
Self-encouragement	17.38	±4.62	16.00–18.77	*t* (44) = −1.46	0.15	−0.22
Therapy compliance	15.64	±3.57	14.57–16.72	*t* (44) = −2.57	0.014[a]	−0.38
Depressive coping	49.11	±15.52	44.45–53.77	*t* (44) = 4.81	<0.001[a]	0.72

Abbreviations: BAI = Beck Anxiety Inventory; BDI = Beck Depression Inventory; FSMC = Fatigue Scale for Motor and Cognitive Function; MMQ = Multifactorial Memory Questionnaire; PSQL = Pittsburgh Sleep Quality Index.
[a] Indicates *p* values 0.001, demonstrating statistically significant results at the 0.1% level (highly significant).
[b] Indicates *p* values < 0.05, demonstrating statistically significant results at the 5% level (significant).

Approximately 36% (18/50) of the patients reported at least mild depressive symptoms, and moderate or severe depressive symptoms were reported by 18% (9/50) of patients (Figure 3A). Similarly, anxiety levels were significantly increased, with at least mild symptoms in 54% (27/50) and moderate or severe anxiety in 28% (14/50) of patients (Figure 3B).

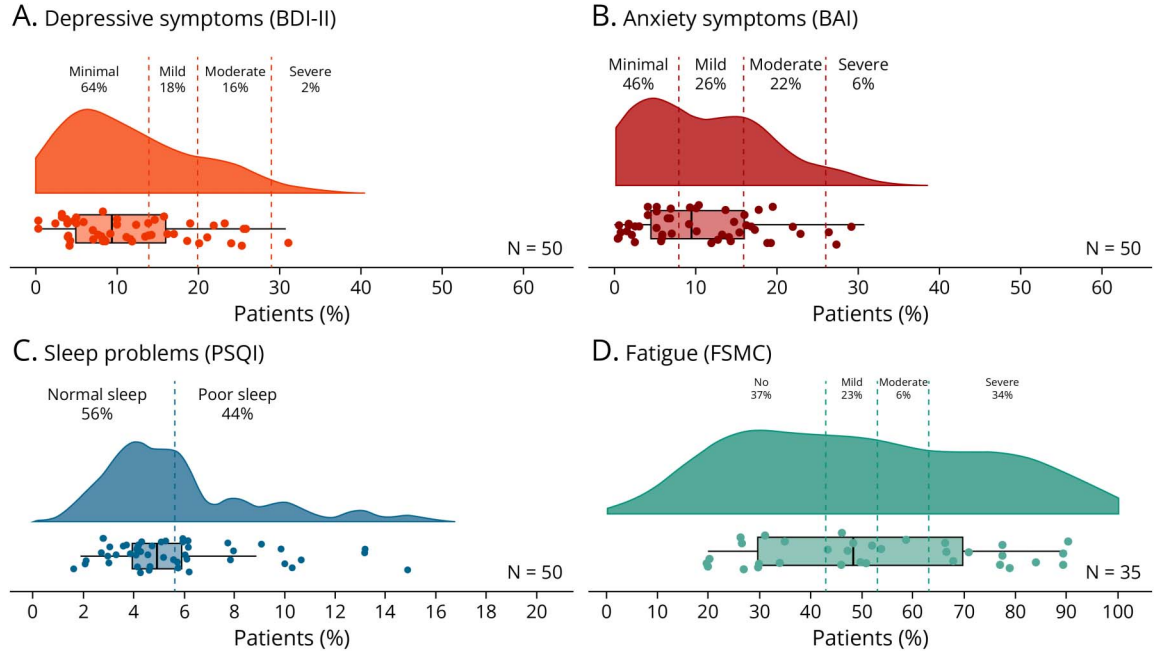
Figure 2 Correlation Plot of Health-Related Quality of Life (HRQoL) With (A) Long-Term Symptoms and (B) Disease Coping Behaviors in Patients With Anti-NMDAR Encephalitis



(*$p < 0.05$, **$p < 0.01$, ***$p < 0.001$). In Panel A, significant negative correlations are observed between HRQoL and long-term symptoms, particularly cognitive fatigue, sleep problems, and memory satisfaction, as well as depressive and anxiety symptoms. By contrast, the physical domain of HRQoL presents a more complex picture, displaying variable degrees of correlation with a variety of symptoms. Panel B reveals that positive coping behaviors, notably self-efficacy and self-encouragement, are positively associated with HRQoL, whereas negative coping behaviors, such as resignation, are strongly negatively associated with HRQoL, indicating that a tendency to give up or feel helpless is linked with poorer patient-reported outcomes in quality of life.

Sleep problems affected 44% (22/50, PSQI >5) of the patients (Figure 3C) and were the only variable that was associated with time since onset ($r = 0.35$, $p = 0.02$, n = 45). Sleep quality was particularly compromised by sleep disturbances (i.e., waking up during the night; 96%, 48/50), reduced subjective sleep quality (88%, 44/50), increased

Figure 3 Neuropsychiatric Scales With Cutoffs for Symptom Severity of Affective Changes, Sleep Quality, and Fatigue in Postacute Patients With Anti-NMDAR Encephalitis



sleep latency (i.e., not falling asleep within 30 minutes; 86%, 43/50), and daytime dysfunction (76%, 38/50 of the patients reporting difficulties). On the BDI-II sleep item, an increased need for sleep was more common (48%, 24/50) than a decrease (30%, 15/50). Fatigue levels were significantly increased (Figure 3D). Approximately 63% (22/35) reported at least mild fatigue, and fatigue was severe in 34% (12/35) of the patients. Cognitive fatigue and motor fatigue (none: 43%/40%, mild: 17%/17%, moderate: 9%/9%, severe: 31%/34%) were equally affected.

Metacognitive Scales

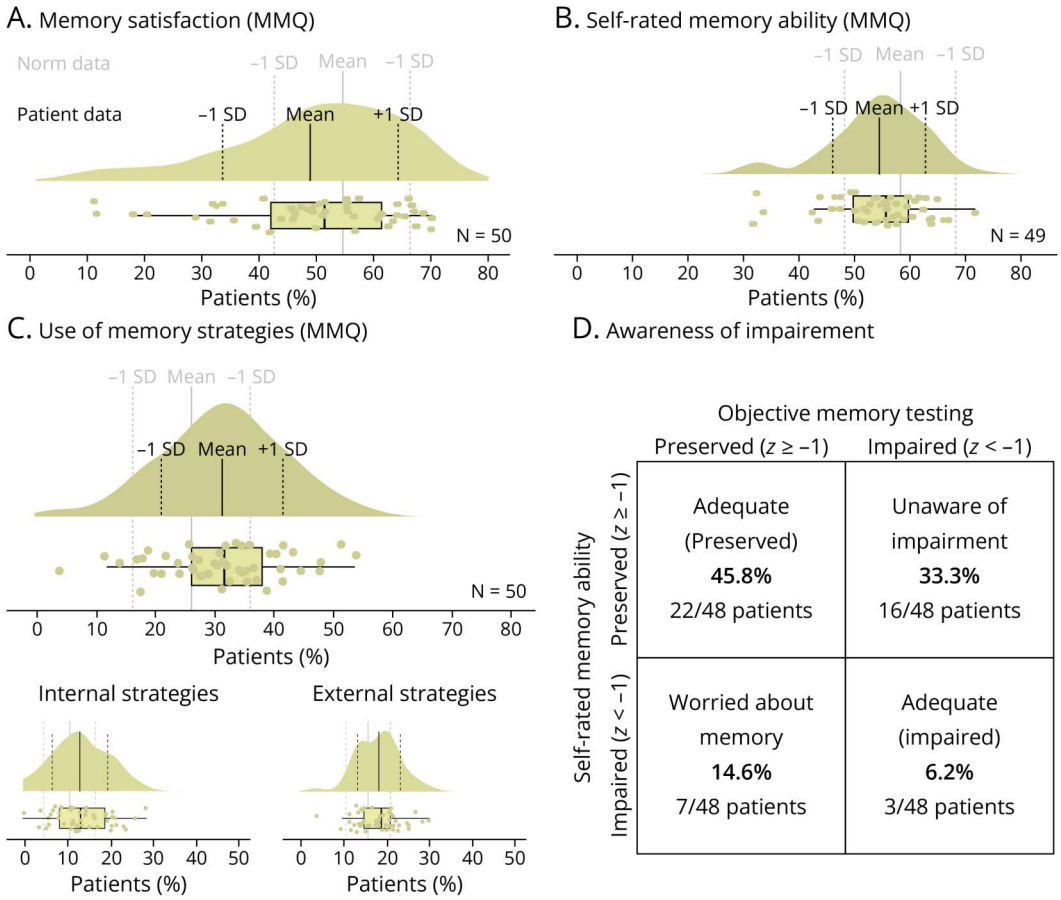
Memory Satisfaction

Subjective satisfaction with everyday memory was significantly decreased in the follow-up of NMDAR encephalitis (Figure 4). Notable concerns of the patients related to a subjective deterioration of memory (3.32 ± 0.8), being embarrassed of their memory (3.40 ± 0.8), and being worried about their memory (3.10 ± 0.8). In this study, memory satisfaction was unrelated to objective working memory (r = 0.17, p = 0.24, n = 48), short-term memory (r = 0.23, p = 0.11, n = 48), and long-term retention scores obtained during neuropsychological testing (r = 0.09, p = 0.57, n = 47).

Memory Ability

After NMDAR encephalitis, patients rated their subjective memory function in everyday life significantly lower than the normative population (Figure 4B). Self-reported memory errors occurred most frequently during word finding (2.24 ± 0.7), remembering a telephone number (2.27 ± 0.8), recalling names of recently met people (2.35 ± 0.8), and forgetting to bring an item (2.35 ± 0.7). Again, self-rated memory ability was not related to neuropsychological test scores of working memory (r = 0.009, p = 0.55, n = 47), short-term memory (r = −0.04, p = 0.78, n = 47), and long-term retention (r = −0.17, p = 0.25, n = 46). However, 33.3% (16/48) of the patients rated their memory ability as normal (−1 < z < +1) despite a low performance on the verbal memory test (i.e., these patients were unaware of their impairment) (Figure 4D). By contrast, only 3 patients (6.2%) with objective verbal memory impairment also reported memory problems. Similar proportions were observed for working

Figure 4 Decreased Satisfaction With Memory and Perceived Everyday Memory Ability in Patients With Anti-NMDAR Encephalitis



Raincloud plots illustrating the distribution of patient scores of the MMQ subscales. Gray vertical lines denote the mean and SD of the German normative data while black vertical lines indicate the mean and SD of the patient cohort. MMQ = Multifactorial Memory Questionnaire.

memory; i.e., 31.2% (15/48) of patients assessed were unaware of their impairment although they performed poorly on the working memory test. Conversely, only 4 patients (8.3%) expressed concerns about their memory regardless, which coincided with the objectively assessed deficits in working memory (eFigure 3).

Memory Strategies

Patients used memory strategies significantly more frequently than the general population (Figure 4C). Frequently used external memory aids included calendars (3.16 ± 0.7), writing lists (2.70 ± 0.8), and using routines (2.54 ± 1.0). Internal memory strategies that were most frequently used were mentally retracing steps (2.10 ± 0.9), intentionally concentrating (1.88 ± 0.8), and saying something out loud (1.82 ± 1.0). Overall, internal strategies were used significantly less often than external strategies (t [98] = -4.64, $p < 0.001$). Lower confidence in memory abilities was associated with more extensive use of strategies ($r = -0.41$, $p = 0.004$, n = 49).

Disease Coping Scales

Regarding adaptive behaviors and cognitions, we observed no difference in self-efficacy between patients with NMDAR encephalitis and the normative population (Table). However, patients made greater use of general positive stress coping strategies, such as positive self-instruction (t [49] = 2.44, $p = 0.02$) and seeking social support (t [49] = 2.37, $p = 0.02$). By contrast, when compared with a non-neurologic reference sample of dialysis patients and patients with breast cancer, patients with encephalitis were less likely to use cognitive coping mechanisms, such as problem analysis (t [45] = -2.44, $p = 0.02$), relativization (t [44] = -3.54, $p = 0.001$), or therapy compliance (t [44] = -2.57, $p = 0.01$), but were more likely to use depressive disease coping (t [44] = 4.81, $p < 0.001$).

Predictors of HRQoL

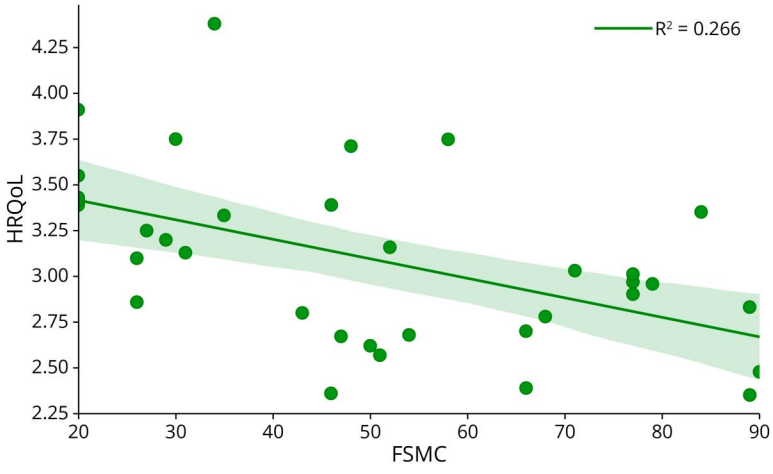
Anxiety ($\beta = -0.02$, $p = 0.03$) and depressive symptoms ($\beta = -0.34$, $p = 0.001$) significantly predicted HRQoL after NMDAR encephalitis (Model 1; $F(5, 44) = 16.5$, $p < 0.001$, $R^2_{adjusted} = 0.62$; eTable 8). Using a simple linear regression model (Figure 5), fatigue was found to significantly predict quality of life ($\beta = -0.01$, $p = 0.03$) with a modest goodness of fit ($F = 11.95$, $p < 0.001$, $R^2_{adjusted} = 0.24$). Regarding disease coping behaviors, self-efficacy ($\beta = 0.01$, $p = 0.03$) and negative stress management ($\beta = -0.03$, $p < 0.001$) were significant predictors of long-term well-being (*Model 2*; $F(4, 45) = 5.66$, $p < 0.001$, $R^2_{adjusted} = 0.28$; eTable 9). By contrast, none of the variables of the acute disease phase predicted long-term outcomes (*Model 3*; eTable 10).

In addition, neither current medication use such as antipsychotics ($F = 1.65$, $\beta = -0.62$, $p = 0.21$, $R^2_{adjusted} = 0.01$) or anticonvulsants ($F = 0.22$, $\beta = -0.11$, $p = 0.64$, $R^2_{adjusted} = -0.02$), the occurrence of relapses ($F = 0.64$, $\beta = 0.09$, $p = 0.63$, $R^2_{adjusted} = -0.016$), nor the presence of other diseases ($F = 1.0$, $\beta = -0.15$, $p = 0.32$, $R^2_{adjusted} = 0.0$) significantly correlated with HRQoL (eFigure 4).

Discussion

In this cross-sectional study, we show that patients recovering from NMDAR encephalitis experience lower HRQoL and increased levels of neuropsychiatric symptoms, including postacute depressiveness, anxiety, sleep problems, and fatigue. Moreover, metacognitive ratings revealed that persistent subjective memory concerns were common and led to a greater dependence on compensatory memory strategies. Of interest, postacute HRQoL was decoupled from the severity of the acute phase. Instead, quality of life was predicted by self-reported affective symptoms and adaptive disease coping

Figure 5 Association Between Fatigue Scale for Motor and Cognitive Functions (FSMC) Scores and Health-Related Quality of Life (HRQoL)



Scatterplot illustrating the negative correlation between FSMC scores and HRQoL, indicating that higher levels of fatigue as measured by the FSMC are associated with lower perceived quality of life. Each point represents an individual participant's scores. The green line represents the best-fit linear regression line (y = −0.01x + 3.63), with the shaded area depicting the 95% CI for the regression estimate.

behaviors. These findings characterize the neuropsychiatric long-term profile of NMDAR encephalitis and identify potentially modifiable treatment targets.

After a median of 4.15 years after the acute disease, HRQoL was significantly impaired in patients with NMDAR encephalitis and affected physical, social, and cognitive-emotional domains, even in the late phases of recovery (i.e., 5.6–30.3 years since onset). This finding aligns with and extends previous work showing reduced quality of life, especially in the social domain, at a median of 77.5 months after onset.[24] A major predictor of low quality of life in our sample was persistent depressive and anxiety symptoms. During the acute phase, psychiatric symptoms in NMDAR encephalitis are best described as a mixed mood-psychosis phenotype.[25] In our follow-up sample, around 60% of the patients experienced at least mild anxiety, with moderate-to-severe symptoms in around 30% of patients. In addition to pathologic brain changes to areas involved in mood regulation, such as microstructural integrity impairment and volume loss in the hippocampus and amygdala,[26-28] disease-related experiences may contribute to the emergence of affective symptoms. Indeed, qualitative studies have shown that social and emotional consequences of the disease can interact with long-term symptoms: while traumatic acute phase experiences and fear of relapse and isolation worsened anxiety, these higher anxiety levels were a cause of social avoidance themselves.[20,21]

We, furthermore, observed increased levels of depressive symptoms after NMDAR encephalitis compared with the general population. Mild depressive symptoms occurred in approximately 36% of the patients, and 18% experienced moderate-to-severe depressiveness, corroborating 2 recent studies on depressive symptoms in patients with different autoimmune encephalitis variants[10] and in a sample of patients with NMDAR encephalitis,[29] highlighting depression as a major symptom in the postacute phase of the disease. Accordingly, patients used depressive coping strategies more frequently and were less likely to use more favorable cognitive coping mechanisms, such as relativization and problem analysis. Furthermore, increased depressiveness was one of the main predictors of postacute quality of life. This is in line with previous research in patients with acquired brain injury, where depressiveness was found to be the best predictor of psychosocial outcomes[30] and was associated with avoidant disease coping, i.e., emotion-focused strategies that can include denial, cognitive disengagement, or social withdrawal.[31] Both disease-related critical life events and the challenge to develop effective coping strategies while tackling comorbid mood disorders have been discussed to contribute to depressiveness after acquired brain injuries[30,31] and likely apply to a severe neurologic disease like NMDAR encephalitis as well. This is important for 2 reasons: On the one hand, mood disorders constitute a potentially treatable comorbidity in patients recovering from NMDAR encephalitis. On the other hand, a follow-up with a psychiatrist has been shown to increase the odds of returning to school or work in patients with autoimmune encephalitis,[19] thus allowing patients to regain postacute independence.

Sleep problems were common in the postacute phase of NMDAR encephalitis and affected 44% of the patients in our study. Patients frequently reported difficulties to fall asleep (86%), waking up during the night (96%), and daytime dysfunction (76%). These findings align with a recent study in which polysomnography and comprehensive sleep assessment revealed higher levels of sleep dysfunction, increased daytime sleepiness, and more frequent confusional arousals in non-REM sleep in patients recovering from NMDAR encephalitis compared with healthy controls.[9] Of interest, this study also reported a pattern of insomnia during the acute phase and hypersomnia during the recovery phase. Although our patient sample was studied at a median of 4.15 years after onset and thus later than the patients in the previous study (median of 183 days after onset), we likewise observed that an increased need for sleep was more common (48%) than a decreased need for sleep (30%). Sleep disturbances were also the only variable that was associated with time since onset. Sleep problems in postacute autoimmune encephalitis have only recently started to gain attention[9,11-13,32] but can occur independent of symptomatic medication and are thus argued to be a symptom of the disease rather than a mere adverse treatment effect.[13]

Our analyses, furthermore, show that patients with NMDAR encephalitis experience increased levels of fatigue during recovery. Both cognitive fatigue and motor fatigue were equally affected, a third of the patients experiencing severe fatigue. It is important to note that fatigue predicted quality of life, with higher fatigue levels being associated with decreased quality of life. Indeed, recent studies indicate that fatigue is a common comorbidity after autoimmune encephalitis,[10,32,33] and a study in children with NMDAR encephalitis showed that fatigue is strongly correlated with HRQoL.[34] Moreover, fatigue is a common symptom in other neuroimmunologic disorders including multiple sclerosis[35,36] and post–COVID-19 syndrome[37] and has been associated with structural damage[38,39] and altered functional connectivity.[38,40,41] In these disorders, fatigue is linked to higher rates of depression,[42,43] increased anxiety,[43,44] and sleep disturbances.[42] Indeed, we observed the same symptoms in our sample of patients with NMDAR encephalitis, highlighting the need to further study their pathophysiologic links.

Memory and concentration difficulties were the most frequently reported subjective symptoms in our study. It is important to note that around 33% of the patients reported normal subjective memory abilities despite impaired performance on an objective verbal memory test; i.e., these patients were not aware of their memory impairment. However, overall, patients in our sample had significantly reduced memory satisfaction and self-rated memory abilities that were not linked to objective test scores. In this study, it is important to note that metamemory is a multidimensional construct that includes both personal appraisal and the regulation of memory processes[23] and subjective memory ratings do not necessarily reflect objective cognitive performance and can be subject to biases in both health and disease. Our findings thus

highlight the complex interplay between neuropsychiatric and cognitive long-term symptoms in NMDAR encephalitis.

In summary, our findings have relevant implications for the long-term management of cognitive dysfunction in NMDAR encephalitis. First, formal neuropsychological testing is an essential part of follow-up care in these patients, even if they do not report memory problems during follow-up visits. Second, patients who used more memory strategies more frequently reported worse subjective abilities. The management of memory deficits in cognitive rehabilitation should, therefore, emphasize the use of memory aids and daily life management strategies.[45,46] This also underscores the necessity for long-term postacute care of memory deficits beyond early rehabilitation, for instance, in ambulatory neuropsychological settings.[21] Third, managing memory deficits after NMDAR encephalitis should take potential co-occurring neuropsychiatric symptoms into account because they can influence a patient's memory appraisal and affect the effectiveness of intervention programs.[46]

Current recommendations for the postacute care of patients with autoimmune encephalitis include close follow-ups after the acute phase and yearly follow-ups once the patient is stable.[47,48] Our study shows that patients with NMDAR encephalitis experience a diverse spectrum of postacute symptoms. This highlights the need for multidisciplinary care that is tailored to the patients' individual needs, involving psychiatrists, neurologists, psychotherapists, neuropsychologists, and speech or occupational therapists. This need becomes even more evident when considering the young age of most patients with NMDAR, where it has been shown that younger age in patients with NMDAR encephalitis can be associated with worse long-term adaptive behaviors.[49] To support emotional and cognitive recovery and increase quality of life, rehabilitation should ideally focus on real-life problems and set specific and achievable goals.[46] These goals will typically differ between individuals, ranging from restoring functions to functional adaptation and more efficient use of residual skills.[50] Our analyses show that patients were more likely to engage in depressive coping behaviors after NMDAR encephalitis. A potential target for behavioral therapy in these patients is, therefore, to focus on the less frequently used cognitive coping strategies, such as problem analysis and relativization, and limit depressive coping.[46] Other studies have further identified social support systems and positive interactions with health care professionals as beneficial for recovery.[20] Clear and consistent communication during care transitions, starting in the acute care hospital, was found to be particularly relevant to disease-related and caregiver burden.[21,32]

While our study provides a comprehensive assessment of postacute symptoms and disease coping in NMDAR encephalitis, several limitations need to be acknowledged. The median time since onset in this analysis was 4.15 years, ranging from 3 months to 30.3 years since the onset of the first encephalitis-related symptoms. Although this range in disease duration is considerable, it allows assessment of a wide spectrum of patients and stages of recovery at the same time. Indeed, our explorative analyses in which we stratified the patient cohort into 3 consecutive periods after disease duration indicated that patients with NMDAR encephalitis continue to experience increased affective symptoms, poorer sleep quality, and fatigue even many years after disease onset (a more detailed discussion in eMethods 1). This observation emphasizes that postacute symptoms can persist for several years after the acute disease. In addition, the assessment of fatigue was introduced only at a later study stage, resulting in fatigue data being obtained from only 70% of patients. Nevertheless, we observed robustly increased fatigue levels in patients and a robust relationship between higher fatigue scores and reduced quality of life. Moreover, we assessed anxiety and depressive symptoms using self-reported questionnaires and screening tools. While these are helpful in determining the self-reported frequency and severity of such symptoms, they do not replace a formal diagnosis by psychiatrists or psychotherapists. Finally, affective symptoms may be a sign of the autoimmune encephalitis itself, may originate from maladaptive coping after a potentially life-threatening brain disease and experiencing respective lifestyle disruptions, or both. Owing to the cross-sectional and correlational nature of these analyses, establishing cause-effect relationships and interactions is not feasible.

We show that patients experience ongoing neuropsychiatric and cognitive symptoms in the postacute phase of NMDAR encephalitis that significantly affect their quality of life. Specifically, subjective memory concerns and sleep problems are common, and patients report increased levels of fatigue, depressiveness, and anxiety. These long-term symptoms were not related to the severity of the acute disease and the low postacute physical disability seen in standard clinician-assessed scales. Taken together with behavioral disease coping strategies, these findings highlight potentially modifiable treatment targets and the need for continuous screenings during follow-up care. In addition, they underline the importance to include patient-reported measures as outcomes in clinical trials to improve long-term outcomes and patient well-being in autoimmune encephalitis.

Author Contributions

J. Heine: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; study concept or design; analysis or interpretation of data. O.J. Boeken: drafting/revision of the manuscript for content, including medical writing for content; analysis or interpretation of data. S. Rekers: drafting/revision of the manuscript for content, including medical writing for content; analysis or interpretation of data. K. Wurdack: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data. H. Prüss: drafting/revision of the manuscript for content, including medical writing for content; major role in the

acquisition of data. C. Finke: drafting/revision of the manuscript for content, including medical writing for content; study concept or design.

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