Long-Term Cognitive Outcome in Anti–N-Methyl-D-Aspartate Receptor Encephalitis

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Objective: Cognitive dysfunction is a core symptom of anti–N-methyl-D-aspartate receptor (NMDAR) encephalitis, but detailed studies on prevalence, characteristics of cognitive deficits, and the potential for recovery are missing. Here, we performed a prospective longitudinal study to assess cognitive long-term outcome and identify clinical predictors.
Methods: Standardized comprehensive neuropsychological assessments were performed in 43 patients with NMDAR encephalitis 2.3 years and 4.9 years (median) after disease onset. Cognitive assessments covered executive function, working memory, verbal/visual episodic memory, attention, subjective complaints, and depression and anxiety levels. Cognitive performance of patients was compared to that of 30 healthy participants matched for age, sex, and education.
Results: All patients had persistent cognitive deficits 2.3 years after onset, with moderate or severe impairment in >80% of patients. Core deficits included memory and executive function. After 4.9 years, significant improvement of cognitive function was observed, but moderate to severe deficits persisted in two thirds of patients, despite favorable functional neurological outcomes (median modified Rankin Scale = 1). Delayed treatment, higher disease severity, and longer duration of the acute phase were predictors for impaired cognitive outcome. The recovery process was time dependent, with greater gains earlier after the acute phase, although improvements were possible for several years after disease onset.
Interpretation: Cognitive deficits are the main contributor to long-term morbidity in NMDAR encephalitis and persist beyond functional neurological recovery. Nonetheless, cognitive improvement is possible for several years after the acute phase and should be supported by continued cognitive rehabilitation. Cognition should be included as an outcome measure in future clinical studies.

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Cognitive dysfunction is a core symptom in patients with anti–N-methyl-D-aspartate receptor (NMDAR) encephalitis.[1,2] Impairments of cognitive function substantially affect the quality of life, potential academic and occupational achievements, and social interactions of the frequently young patients.[3] Here, we present the first comprehensive longitudinal study of the cognitive sequelae of NMDAR encephalitis in adults based on detailed neuropsychological assessments.

Following the first description of NMDAR antibodies 13 years ago,[4] clinical studies have started to examine the long-term prognosis in patients with NMDAR encephalitis. Large-scale studies assessed neurological outcomes based on the modified Rankin Scale (mRS)[1,5] and

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cognitive screening results—such as the Mini-Mental State Examination (MMSE)[5]—for a follow-up period of up to 24 months. With a definition of a good outcome as an mRS score ≤ 2, which characterizes a status of relative independence in most activities of daily living while still experiencing slight disabilities,[6] about 80% of the patients showed full recovery or improved to mild deficits within 2 years of follow-up.

Considering the severe disease course in many patients, which frequently requires intensive care unit admission and can include autonomic instability, status epilepticus, or coma,[7] neurological long-term outcome appears to be relatively favorable. However, clinical outcome measures like the mRS focus on physical impairment and largely neglect cognitive dysfunction, despite its substantial and permanent impact on daily functioning. Patients with NMDAR encephalitis often report self-observed residual deficits in the postacute phase that span several cognitive domains and manifest in poor memory,[3,8,9] difficulties concentrating on everyday tasks,[3,8–10] increased fatigability,[8,10] and social withdrawal.[8] Neuropsychological studies have revealed impairments in the majority of these patients, with deficits encompassing episodic and working memory[2,3,8–14] as well as executive function.[2,3,8–14] In addition, deficits of attention,[2,3,8–10,12,13] language deficits,[9,10] and visuospatial dysfunction[8] can occur.

Considering the typically young age at onset in NMDAR encephalitis, promoting cognitive recovery is essential for preserving the patients' potential at school, at university, or at the workplace. Previous small case series point to a potential recovery in some patients and domains, whereas others continue to have persistent impairment.[2,10,12,13] However, cross-sectional study designs, short follow-up times, small sample sizes, and differences in testing protocols and analyses impede coherent conclusions.

We therefore performed a comprehensive longitudinal neuropsychological and clinical assessment in 40 patients with NMDAR encephalitis at 2 time points. The aims of this study were to (1) systematically investigate the cognitive outcome in a large sample of NMDAR encephalitis patients, (2) describe the trajectory of cognitive deficits in a 2-year follow-up, (3) explore the relationship between clinical neurological and cognitive recovery, (4) identify clinical predictors of cognitive long-term outcome, and (5) evaluate the time courses of recovery of cognitive function across the major cognitive domains.

Subjects and Methods

Participants

We prospectively enrolled 43 adult patients with NMDAR encephalitis to participate in 2 follow-up study visits between January 2011 and December 2018 (Table 1). We consecutively recruited all available patients from university hospitals in Germany without clinical selection criteria, that is, consecutive patients were enrolled irrespective of their clinical disease course. Three patients with divergent follow-up spans (0.8 years, 1.1 years, and 4.6 years) were excluded from analysis to avoid potential bias due to heterogeneous follow-up times.

All study visits comprised clinical evaluation, comprehensive neuropsychological assessment, and magnetic resonance imaging (MRI) data acquisition conducted at the Department of

TABLE 1. Patient Characteristics

Study Participation	Patients, First Visit	Patients, Second Visit	Controls
Sex, n (% F)	35 F/5 M (88%)	35 F/5 M (88%)	25 F/5 M (83%)
Age, yr, mean ± SD (range)	28.5 ± 7.2 (15–45)	30.7 ± 7.2 (17–48)	30.1 ± 8.3 (16–52)
Education, yr, mean ± SD (range)	13.5 ± 2.0 (10–18)	14.0 ± 1.7 (10–18)	14.4 ± 2.0 (10–18)
mRS, median (range)	1 (0–3)	1 (0–1)	—
Time since disease onset, yr, median[a]	2.3 (0.3–7.0)	4.9 (2.3–9.4)	—
Subjective cognitive complaints, n (%)	29/40 (73%)	20/40 (50%)	0/30 (0%)
Anticonvulsants, n (%)[b]	6/40 (15%)	2/40 (5%)	—
Antipsychotics, n	0/40	0/40	—
Time between visits, yr, median	2.1 (1.7–2.8)		—

[a]Time span between symptom onset and study date.

[b]Anticonvulsants included levetiracetam, valproate, lamotrigine, and oxcarbazepine exclusively (n = 4) or in combination (n = 2).

No significant difference in cognitive performance between patients with and without anticonvulsants was observed at first (CS: median 3.5 (1–5) vs 3.5 (1–5), $U = -0.098$, $p = 0.93$) and second visit, where only two patients received anticonvulsants (scores 1 and 4 vs 2.5 (0–4)).

Neurology at Charité–Universitätsmedizin Berlin and the Berlin Center for Advanced Neuroimaging. All patients tested NMDAR antibody-positive in cerebrospinal fluid (CSF) during the acute disease phase and fulfilled the current diagnostic criteria.[15] Clinical details are provided in Table 2. Neurologic disability was assessed using the mRS. Patients were frequency matched to a group of 30 healthy controls without history of neurological or psychiatric disease with regard to sex, age, and education (see Table 1). This study was approved by the ethics committee of Charité–Universitätsmedizin Berlin. Written informed consent was obtained from all participants in accordance with the Declaration of Helsinki.

Neuropsychological Assessment

All participants underwent an extensive neuropsychological test battery covering the 5 cognitive domains of (1) executive function, (2) working memory, (3) verbal and (4) visual episodic memory, and (5) attention. We assessed (1) executive function using a Go/No-Go[16] and Stroop[17] paradigm (Farbe-Wort-Interferenztest). In a semantic fluency test, participants were moreover asked to name as many animals as possible within 1 minute (Regensburger Wortflüssigkeitstest[18]). Working memory (2) was examined with the forward and backward conditions of the digit span test (Wechsler Adult Intelligence Scale IV[19]). Tests of episodic memory included (3) a word list learning paradigm (Verbaler Lern- und Merkfähigkeitstest,[20] German version of the Rey Auditory Verbal Learning Test) for the verbal and (4) the Rey–Osterrieth Complex figure test (36-point scoring system) for the visual domain. Both tests include a short-term and delayed recall. Lastly, we examined (5) attention using a cued and noncued reaction time task (subtests phasic and tonic alertness) as well as a dual-task paradigm with simultaneous auditory and visual cues (subtest divided attention) from the Testbatterie für Aufmerksamkeitsprüfung.[16] Response times and error rates were recorded. We additionally included an estimate of premorbid intelligence levels (Mehrfachwahl-Wortschatz-Intelligenztest[21]). Parallel test versions were used for longitudinal testing as appropriate. Details about subjective cognitive deficits, and mental and physical state were recorded using structured interviews. In addition, patients performed a self-report depression (Beck Depression Inventory II[22]) and anxiety screening (Beck Anxiety Inventory[23]).

Statistical Analyses

Cross-Sectional Analyses. First, we investigated the overall frequency of cognitive impairment at first and second study visit. Raw test scores of each patient were *z*-standardized with regard to the mean and standard deviation of the control group. Performance on a neuropsychological test was considered impaired when a patient performed ≤1 standard deviation (SD) below controls (see Table S1 for −1.5 SD). A deficit at the domain level was detected when patients showed impairments in at least one test of the respective domain. Besides determining the prevalence of cognitive impairment, this allowed us to identify cognitively affected patients. Furthermore, a composite score of cognitive dysfunction was defined as the number of affected domains. The Shapiro–Wilk test was used to assess the normality of the data. We used lme4[24] in R for a linear mixed effects analysis of the relationship between cognitive performance and study visit. By modeling intercepts for subjects and time since onset as random effects, we accounted for baseline differences between individuals and variation in timing of the neuropsychological assessments after the acute phase. Probability values are 2-tailed and adjusted for multiple comparisons using the Benjamini–Hochberg correction. Statistical analyses were carried out using SPSS Statistics (IBM, Armonk, NY) and R 3.6.1.

Longitudinal Analyses. Second, we assessed the longitudinal evolution of cognitive performance using McNemar tests for the proportion of affected patients in each domain. Additionally, we analyzed the longitudinal development of deficits in cognitively impaired patients as identified in the cross-sectional analysis of the first study visit. Changes in cognitive performance were tested using the Wilcoxon signed-rank test for repeated measurements.

Regression Analyses. Multiple linear regression analysis was used to identify clinical predictors for cognitive outcome. The following variables were included as log-transformed predictors for long-term cognitive performance: (1) time between disease onset and initiation of treatment (treatment delay; days), (2) total duration of hospitalization in acute neurological care (days), (3) intensive care unit (ICU) treatment, (4) maximal mRS score during the acute disease phase, and (5) age of onset (years).

Temporal Evolution of Recovery. To explore the temporal dynamics of recovery from cognitive impairment, we performed linear regression and correlation analyses between recovery time (time between disease onset and last study visit) and longitudinal change in cognitive performance (change in composite score, change in performance across domains [SD]).

Results

Clinical Symptoms and Subjective Cognitive Complaints

The patient group was typical of NMDAR encephalitis with respect to acute phase symptoms, demographic characteristics, and disease course variables, including ICU admission, administered first- and second-line therapies, and MRI and electroencephalographic abnormalities. Further clinical characteristics are provided in Table 2. Detailed antibody titers and CSF findings are presented in Table S2. Despite moderate to severe disability during the

TABLE 2. Clinical Characteristics

Disease course			
Age at onset, yr, **mean ± SD** (range)	25.9 ± 7.1 (15–44)	**Maximum mRS, median (range)**[a]	4 (2–5)
Acute phase MRI abnormalities, n (%)	**18/40 (45%)**	**Acute phase EEG abnormalities, n (%)**	25/40 (63%)
White matter lesions, n (%)	12/40 (30%)		
Mesiotemporal T2 hyperintensity, n (%)	3/40 (8%)		
Mild global atrophy, n (%)	3/40 (8%)	**Depression [BDI-II], median (range)**	8 (0–24)
Basal ganglia T1 hyperintensity, n (%)	1/40 (3%)	**Anxiety [BAI], median (range)**	12 (0–27)
Symptoms			
Prodromal symptoms, n (%)	**22/40 (55%)**	**Acute phase symptoms, n (%)**	**40/40 (100%)**
Affective/personality change, n (%)	19/40 (48%)	Neuropsychiatric, n (%)	39/40 (98%)
Influenza-like symptoms, n (%)	12/40 (30%)	Cognitive, n (%)	38/40 (95%)
		Seizures, n (%)	29/40 (73%)
Tumor, n (%)[b]	10/40 (25%)	Sleep disorder, n (%)	20/40 (50%)
Relapse, n (%)[c]	7/40 (17.5%)	Movement disorder, n (%)	17/40 (43%)
Treatment delay, days, median (range)[d]	31 (1–770) d	Autonomic dysfunction, n (%)	13/40 (33%)
		Status epilepticus, n (%)	3/40 (8%)
Acute phase treatment			
Acute neurological care, n (%)	**40/40 (100%)**	**Intensive care unit, n (%)**	**23/40 (58%)**
Days in neurological care, median (range)	83 (15–410)	Days in ICU care, median (range)	19 (1–252)
First-line therapy, n (%)	**39/40 (98%)**	**Second-line therapy, n (%)**	**6/40 (15%)**
IV methylprednisolone, n (%)	32/39 (82%)	Rituximab, n (%)	5/40 (13%)
Therapeutic apheresis, n (%)	26/39 (67%)	Cyclophosphamide, n (%)	32/40 (80%)
IV immunoglobulins, n (%)	24/39 (62%)	Azathioprine, n (%)	23/40 (58%)
Oral prednisolone, n (%)	15/39 (38%)		
Anticonvulsants, n (%)	32/40 (80%)	**Antipsychotics, n (%)**	23/40 (58%)

[a]Highest disability score at any time point during the disease.
[b]Tumors included 9 ovarian tumors and 1 testicular teratoma.
[c]Relapses occurred before enrollment (n = 5) or between visits (n = 2) at a median of 21 months (range = 7–44) from onset. Visits were scheduled with an interval of >9 months from acute relapse to ensure that patients had recovered from their relapse. Patients with and without relapse did not differ significantly in their overall cognitive performance at first (CS: $U = -0.357$, $p = 0.751$) and second visit (CS: $U = -1.70$, $p = 0.102$).
[d]Time span between symptom onset and initiation of first-line immunotherapy.
BAI = Beck Anxiety Inventory; BDI-II = Beck Depression Inventory–Second Edition; CS = cognitive composite score; EEG = electroencephalographic; F = female; ICU = intensive care unit; IV = intravenous; M = male; MRI = magnetic resonance imaging; mRS = modified Rankin Scale; SD = standard deviation.

acute phase (median maximum mRS = 4, range = 2–5), the neurological outcomes were favorable; patients showed no or only mild physical disability at the time of first study visit (median of 2.3 years after symptom onset: median mRS = 1, range = 0–3), with further improvement at second study visit (4.9 years after symptom onset: median mRS = 1, range = 0–1). Spontaneous speech production was unremarkable in all patients regarding form and content, with no indication of disordered speech or language. None of the patients reported pain or other potentially compromising physical or psychological stressors during the testing session.

Subjective cognitive complaints were reported by 73% of the patients at first and 50% at second study visit in a structured medical history interview. Perceived deficits were reported for memory and sustained attention, compromising daily activities such as reading, driving, or memorizing new information. Increased fatigability was noted during cognitively demanding tasks in everyday situations. Initially, 11 of 40 (28%) patients reported no complaints despite impaired test performance. Longitudinally, 10 of 40 patients (25%) reported improved, 28 of 40 (70%) unchanged, and 2 of 40 (5%) deteriorated subjective cognition compared to their first study visit.

Cognitive Deficits at First Study Visit

At first study visit 2.3 years after disease onset, all patients had cognitive deficits, with 50% of the patients showing severe cognitive impairment (ie, a composite score of 4–5 affected domains; Fig 1). Another 35% of patients were moderately affected (2–3 affected domains), and only 15% of the patients had mild deficits (1 affected domain). This contrasts with a favorable functional neurological outcome in the majority of patients, with 55% of the patients showing no or only mild disability (mRS = 0–1), 45% having moderate impairments (mRS = 2–3), and none of the patients showing severe disability (mRS = 4–5).

In a linear mixed model accounting for the timing of the first study visit and baseline differences between individuals, patients showed a significantly lower performance on testing of executive function ($p = 0.02$; affected in 80% of the patients), working memory ($p < 0.001$; affected in 75% of the patients), and verbal memory ($p = 0.002$; 72.5%; Fig 2; Table S3; n = 40). Visual memory and attention were affected in 40% and 55% of the patients, respectively, but showed no significant difference. Premorbid intelligence estimates were comparable to those of controls (Table S4).

Cognitive Deficits at Second Study Visit

Improvements of cognitive performance were observed in all patients at second study visit. Here, none of the patients showed deficits across all 5 domains anymore. The proportion of severely affected patients decreased significantly from 50 to 30% at second study visit ($p = 0.021$; see Fig 1). Another 35% of patients remained moderately affected (2–3 domains affected), and 35% of the patients continued to have only minimal deficits (27.5%, 1 domain affected) or had recovered completely (7.5%; see Table S1 for results using a cutoff of ≤ −1.5 SD).

Improvement between first and second study visit was observed across almost all domains, albeit with high rates of patients with persisting deficits at second study visit (see Fig 2A). For example, although the number of patients with executive impairment decreased significantly from 80 to 60% between first and second study visit (see Fig 2B; $p = 0.039$), patients remained significantly below the level of the control group on tests of executive function ($p = 0.035$) when accounting for the timing of study visit and individual baseline differences. Similarly, working memory ($p = 0.007$) and verbal memory ($p = 0.029$) continued to be affected in the overall sample, although the number of

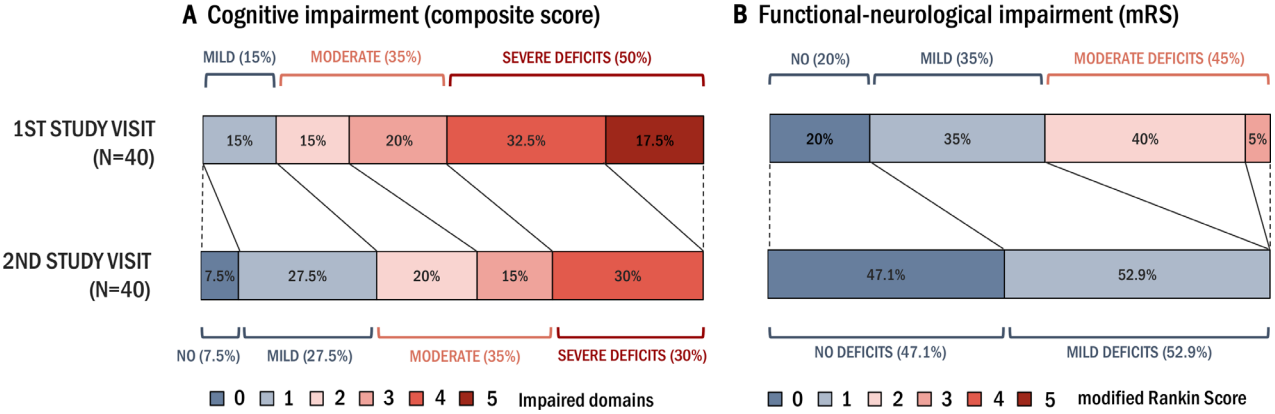

FIGURE 1: Dissociation of cognitive and functional–neurological outcomes in anti–N-methyl-D-aspartate receptor encephalitis. (A) Cognitive impairment at first and second study visit (n = 40). The composite score of cognitive impairment represents the number of affected domains on tests of working memory, verbal and visual episodic memory, executive function, and attention (% of patients). At first study visit (2.3 years after disease onset), 50% of the patients showed severe impairments (4–5 domains affected) and only 15% had mild residual cognitive deficits (1 domain affected). At second study visit (4.9 years after disease onset), 30% of patients continued to have severe cognitive deficits (4–5 domains affected), moderate deficits (2–3 domains affected) persisted in 35% of the patients, and 35% had fully recovered (7.5%) or recovered with only minimal residual impairments (27.5%). (B) In contrast, there was no (20%) or only mild (35%) functional–neurological impairment (modified Rankin Scale [mRS] = 0–1) in 55% of the patients and moderate impairment (mRS = 2–3) in 45% of patients at first study visit. At second study visit, all patients had either fully recovered or had only mild neurological disability. [Color figure can be viewed at www.annalsofneurology.org]

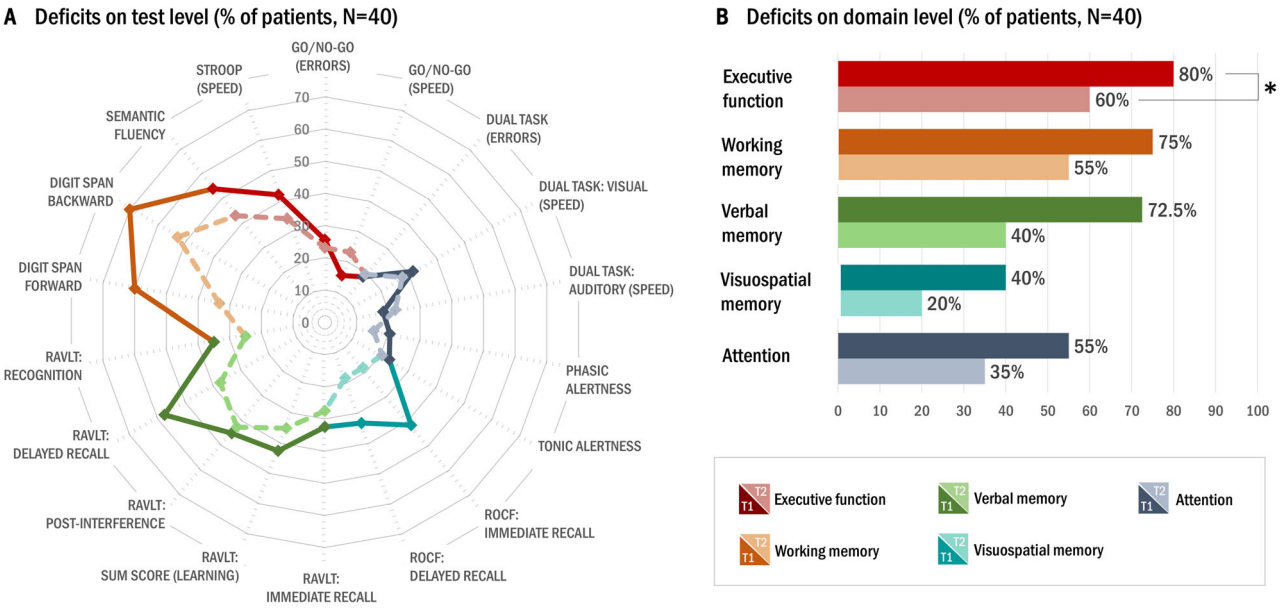

FIGURE 2: Cognitive impairment at first and second study visit at test and domain levels (n = 40). (A) Polar plot showing the percentage of patients with deficits on a test-by-test basis. Cognitive domains are color-coded (see legend). Dark colors represent the first (T1) and light colors the second study visit (T2). (B) Cognitive impairment at the domain level. Bar charts depict percentage of patients with impairment in the respective cognitive domain. Dark colors represent the first (T1) and light colors the second study visit (T2). Cognitive recovery was most pronounced for executive function (80 vs 60%, $p = 0.039$), working memory (75 vs 55%, $p = 0.146$), and verbal episodic memory (72.5 vs 40%, $p = 0.210$). However, residual cognitive deficits were common at second study visit (median = 4.9 years after disease onset), despite this substantial improvement. RAVLT = Rey Auditory Verbal Learning Test; ROCF = Rey–Osterrieth complex figure test. *$p < .05$. [Color figure can be viewed at www.annalsofneurology.org]

affected patients generally decreased (first vs second study visit; working memory: 75 vs 55%, $p = 0.146$; verbal episodic memory: 72.5 vs 40%, $p = 0.210$). Visuospatial memory dysfunction (40 vs 20%, $p = 0.092$) and attention (55 vs 35%, $p = 0.581$) were less common already at first study visit, but also improved in some patients.

Longitudinal Development in Patients with Cognitive Deficits

Next, we analyzed the longitudinal evolution of cognitive deficits for patients with deficits at first study visit (Table 3). Improvements were seen across all cognitive domains, and no deterioration occurred on any of the performed tests. Significant improvement of executive function was demonstrated by better performance on the Go/No-Go test (Wilcoxon signed-rank test: $p = 0.016$, effect size: $r = -0.76$) and the semantic fluency task ($p = 0.04$, $r = 0.50$; Fig 3). Working memory was significantly enhanced for repetition ($p = 0.029$, $r = 0.46$) and manipulation of the material ($p = 0.001$, $r = 0.62$). Verbal memory deficits improved on immediate ($p = 0.009$, $r = 0.73$), postinference ($p = 0.032$, $r = 0.50$), and delayed recall ($p = 0.016$, $r = 0.50$). Visual memory improved on the immediate ($z = 2.36$, $p = 0.018$, $r = 0.59$) but not the delayed condition. In the domain of attention, better performance was reflected in shorter response times ($p = 0.018$, $r = -0.90$) and lower error rates ($p = 0.04$, $r = -0.82$) in the dual-task paradigm. Further analysis of the deficit pattern at first and second study visit showed a strong coexistence of impairments of working memory, verbal memory, and executive function.

Depression and Anxiety Screening

Depression and anxiety screenings revealed no or minimal affective symptoms for most patients (see Table 2) at first study visit. The depression inventory indicated moderate depressive symptoms in 12% of the patients, mild symptoms in 20%, minimal signs in 12%, and no depression in 56%. No association was observed between depressive symptoms and cognitive outcome. Anxiety screening suggested clinically relevant anxiety in 8% of the patients, moderate anxiety in 20%, mild symptoms in 32%, and no or minimal anxiety symptoms in 40%. Stronger symptoms were associated with slower response times on tests of attention ($r = 0.43$, $p = 0.036$).

Predictors of Long-Term Cognitive Outcome

Multiple regression analyses identified several clinical predictors for cognitive outcomes at a median of 4.9 years after the acute phase. Treatment delay significantly predicted long-term executive and memory function, that is, patients with delayed onset of first-line immunotherapy performed worse on testing of inhibition ($b = 0.371$, $t = 2.25$, $p = 0.031$) and verbal episodic memory

TABLE 3. Longitudinal Evolution of Cognitive Deficits

					Longitudinal Evolution			
Domain	**Test**	**Controls**	**First Study Visit**	**Second Study Visit**	**n**	**Test Statistic**	**Effect Size[a]**	**Change**
Executive function	Go/No-Go, median RT, ms	502.3 ± 63.9	612.3 ± 17.8	559.5 ± 52.2	6	$z = -1.57$, $p = 0.116$	$r = -0.64$	→
	Go/No-Go, errors	0.6 ± 0.7	2.6 ± 0.7	1.0 ± 0.9	**10**	**$z = -2.40$, $p = 0.016$[b]**	**$r = -0.76$**	↘
	Stroop, RT	97.7 ± 12.7 s	138.9 ± 19.2 s	126.4 ± 29.2 s	14	$z = -1.35$, $p = 0.177$	$r = -0.36$	→
	Semantic fluency	29.1 ± 5.7	20.4 ± 2.9	23.3 ± 4.5	**16**	**$z = 2.01$, $p = 0.044$[c]**	**$r = 0.50$**	↗
Working memory	Digit span forward	8.6 ± 1.4	5.8 ± 0.8	6.7 ± 1.5	**23**	**$z = 2.19$, $p = 0.029$[b]**	**$r = 0.46$**	↗
	Digit span backward	8.1 ± 1.8	4.9 ± 1.1	6.2 ± 1.2	**26**	**$z = 3.18$, $p = 0.001$[d]**	**$r = 0.62$**	↗
Verbal memory	RAVLT 1, immediate recall	8.9 ± 2.5	4.8 ± 1.1	6.6 ± 1.5	**13**	**$z = 2.62$, $p = 0.009$[d]**	**$r = 0.73$**	↗
	RAVLT sum score, learning	60.8 ± 6.9	44.5 ± 6.2	48.8 ± 7.9	17	$z = 1.73$, $p = 0.084$	**$r = 0.42$**	→
	RAVLT 6, post interference	13.8 ± 1.2	7.5 ± 2.3	9.4 ± 2.6	**18**	**$z = 2.14$, $p = 0.032$[b]**	**$r = 0.50$**	↗
	RAVLT 7, delayed recall	13.5 ± 1.6	8.5 ± 2.0	10.7 ± 3.2	**23**	**$z = 2.41$, $p = 0.016$[b]**	**$r = 0.50$**	↗
	RAVLT recognition[e]	14.8 ± 0.3	11.0 ± 1.6	12.6 ± 1.8	14	$z = 1.80$, $p = 0.071$	**$r = 0.48$**	→
Visual memory[f]	ROCF immediate recall	28.9 ± 2.8	20.1 ± 4.2	26.4 ± 6.1	**15**	**$z = 2.36$, $p = 0.018$[b]**	**$r = 0.61$**	↗
	ROCF delayed recall	29.6 ± 2.8	18.9 ± 4.0	24.8 ± 5.8	12	$z = 1.88$, $p = 0.060$	**$r = 0.54$**	→
Attention	Tonic alertness, median RT, ms	257.7 ± 28.7	336.1 ± 53.0	304.4 ± 42.4	9	$z = -1.72$, $p = 0.086$	$r = -0.57$	→
	Phasic alertness, median RT, ms	269.1 ± 28.3	362.6 ± 60.1	335.0 ± 59.3	8	$z = -1.12$, $p = 0.263$	$r = -0.40$	→
	Dual-task: auditory, median RT, ms	611.1 ± 49.6	771.2 ± 85.9	619.4 ± 36.8	**7**	**$z = -2.37$, $p = 0.018$[b]**	**$r = -0.90$**	↘
	Dual-task: visual, median RT, ms	729.0 ± 64.5	868.8 ± 44.3	782.4 ± 90.0	11	$z = -1.96$, $p = 0.050$	$r = -0.59$	→
	Dual task, errors	1.7 ± 1.7	10.3 ± 6.1	6.3 ± 5.0	**6**	**$z = -2.01$, $p = 0.044$[c]**	**$r = -0.82$**	↘

In patients with deficits on the respective tests at first study visit, Wilcoxon signed-rank tests show significant improvement of memory, executive function, and attention. Scores are presented with mean ± standard deviation.

[a]Rosenthal *r* was used as effect size estimate for the Wilcoxon signed-rank test.

[b]$p < 0.05$.

[c]Not significant after Benjamini–Hochberg correction.

[d]$p < 0.01$.

[e]Corrected for errors.

[f]No patient showed deficits in visuospatial skills.

RAVLT = Rey Auditory Verbal Learning Test; ROCF = Rey–Osterrieth complex figure test; RT = response time.

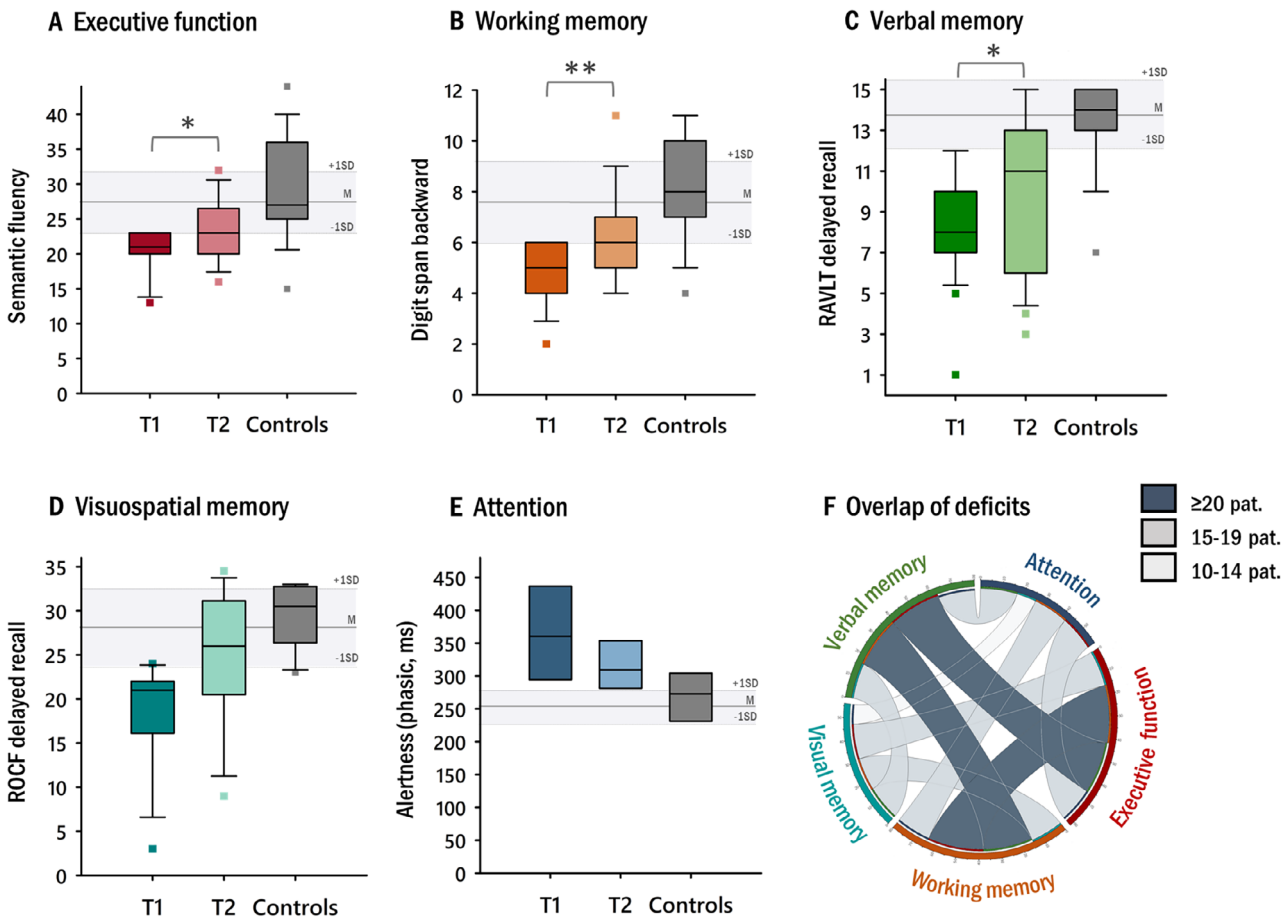

FIGURE 3: Longitudinal development of deficits in representative cognitive tests. (A–E) Patients with deficits of executive function ($z = 2.01$, $p = 0.04$), working memory ($z = 3.18$, $p = 0.001$), and verbal memory ($z = 2.41$, $p = 0.02$) at first study visit improved significantly between the two study visits. *$p < 0.05$, **$p < 0.01$. Solid lines indicate mean (M); dotted lines indicate standard deviation (SD). (F) Overlap of deficits. Circular plot shows a strong coexistence of deficits in working memory, verbal memory, and executive function. The strength of the connection between domains represents the number of patients (pat.) presenting with the respective overlap at first study visit. RAVLT = Rey Auditory Verbal Learning Test; ROCF = Rey–Osterrieth complex figure test. [Color figure can be viewed at www.annalsofneurology.org]

($b = -0.436$, $t = -2.81$, $p = 0.008$). Long hospitalization times, that is, a longer duration of the acute phase, significantly predicted working memory outcomes ($b = -0.474$, $t = -2.79$, $p = 0.009$) at our last study visit. Similarly, the disease severity during the acute phase (maximum mRS) predicted visual memory ($b = -0.525$, $t = -3.07$, $p = 0.004$) and the overall cognitive outcome (composite score; $b = 0.536$, $t = 2.90$, $p = 0.006$). The need for ICU admission was associated with a worse visual memory outcome ($b = -0.610$, $t = -3.70$, $p = 0.001$). Lastly, a younger age of onset was associated with a better executive performance at last study visit ($b = 0.345$, $t = 2.20$, $p = 0.035$).

Temporal Evolution of Recovery

Regarding overall cognitive performance, recovery was quantified as the number of recovered domains between first and second study visit. The greatest potential for improvement was observed in patients with severe disease courses, that is, severe cognitive (composite score at first study visit; $r_s = 0.45$, $p = 0.003$) and neurological impairment (maximum mRS; $r_s = 0.37$, $p = 0.02$). Nevertheless, these patients also continued to have more severe residual deficits at second study visit (composite scores; $r_s = 0.53$, $p < 0.001$).

Finally, we analyzed how long cognitive recovery can be observed after disease onset. Improvement of cognitive function was significantly associated with the time point of study visit, that is, cognitive improvement was more pronounced early after the acute phase (composite score; $r_s = -0.41$, $p = 0.009$). To explore this further, we analyzed the recovery patterns in individual cognitive domains (Fig 4). Time-dependent recovery was particularly pronounced for attention ($r = 0.435$, $p = 0.031$), with greater gains early after the acute phase. However, importantly, these analyses also demonstrate that continued improvement of cognitive function is possible for several

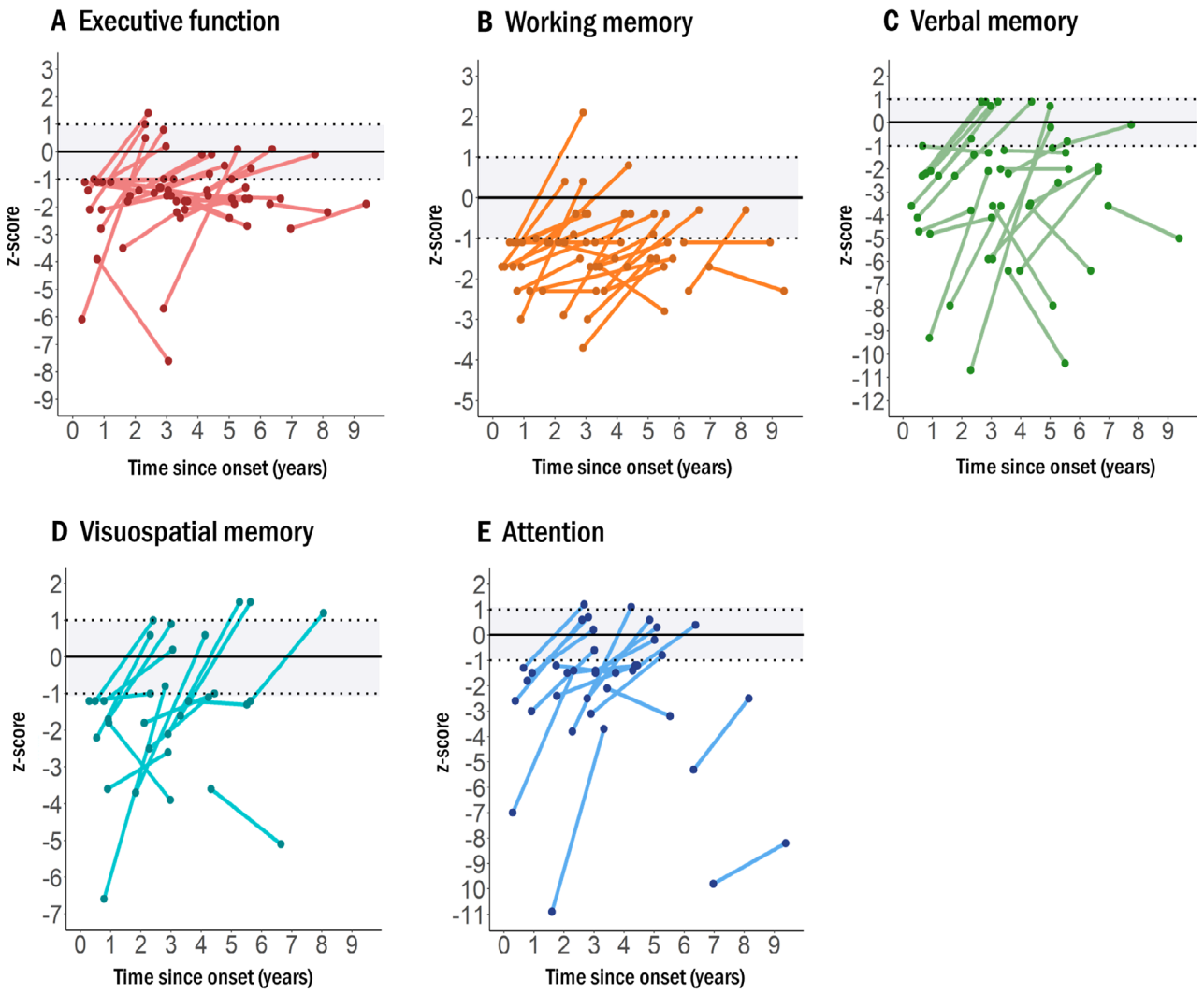

FIGURE 4: Cognitively impaired anti–N-methyl-D-aspartate receptor encephalitis patients show extended periods of cognitive improvement and time-specific recovery patterns. Data points show the trajectory between the first and the second study visit for each patient. [Color figure can be viewed at www.annalsofneurology.org]

years after disease onset (see Fig 4). In a few selected patients, a decrease in cognitive performance was observed. These patients did not suffer from relapses and did not differ from patients with an improved cognitive performance with respect to disease characteristics, for example, disease severity, treatment delay, or treatment strategy.

There was no correlation between the year of disease onset and treatment delay ($r_s = -.264$, $p = 0.137$), cognitive outcome (composite score: $r_s = -.136$, $p = 0.698$), or neurological disability (mRS: $r_s = -.040$, $p = 0.830$) at last study visit, that is, patients who developed NMDAR encephalitis more recently did not have a better long-term outcome.

Discussion

In this comprehensive longitudinal study of cognitive outcome following NMDAR encephalitis, we observed the following main findings: (1) all patients exhibited cognitive deficits after the acute disease stage (median 2.3 years after disease onset), with severe deficits in 50% of patients; (2) core cognitive deficits were impairments of working memory, verbal episodic memory, and executive function; (3) at further follow-up 4.9 years after disease onset, cognitive performance had significantly improved; however, one third of patients continued to have severe deficits, whereas one third was moderately affected and one third had recovered; (4) improvement of cognitive function was seen across all domains; however, working memory, episodic memory, and executive function remained significantly impaired; (5) these persistent cognitive deficits were observed despite a favorable functional neurological outcome; (6) predictors for impaired cognitive long-term outcome were delayed treatment, older age, and higher disease severity, ie higher maximum mRS, longer ICU

treatment, and longer overall disease duration; and (7) importantly, although recovery was time dependent, with greater gains earlier after the acute phase, improvements of cognitive function were observed for several years after disease onset.

Cognitive Impairment Is the Main Contributor to Long-Term Morbidity in NMDAR Encephalitis

All patients had cognitive deficits approximately 2 years after onset, with >80% showing moderate or even severe impairment. This contrasts with the favorable functional neurological outcome in previous observations of large and well-characterized cohorts of NMDAR encephalitis patients.[1,25] Upon further follow-up at a median of 4.9 years after disease onset, patients improved in all cognitive domains, albeit with persisting deficits of memory and executive function. In contrast, all patients had achieved a favorable functional neurological outcome with no or only minor residual disability (mRS = 0–1).

These findings highlight that cognitive impairment is the main contributor to long-term morbidity in NMDAR encephalitis. The dissociation between good functional neurological and poorer cognitive outcome extends findings from earlier small case series suggesting variable cognitive long-term outcomes in NMDAR encephalitis despite substantial improvement or full recovery of other neuropsychiatric symptoms.[2,3,13] Similarly, a recent investigation of long-term cognitive outcome in children with NMDAR encephalitis observed a dissociation between persisting cognitive deficits and good functional outcome 31 months after disease onset.[26]

The high rate of patients with moderate and severe cognitive deficits several years after the disease illustrates the substantial negative impact of the disease on the patients' long-term health. Importantly, these long-lasting cognitive impairments limit the success and participation in occupational and social environments of these typically young patients and thus substantially impact their quality of life. It is therefore important that clinicians are sensitive to cognitive alterations and address complaints in their patients, even when other major neuropsychiatric symptoms have remitted.

Multiple classification systems exist to define cognitive impairment. This study used a sensitive cutoff of −1 SD, corresponding to an impairment of at least mild severity.[27] Considering the sensitivity–specificity trade-off in face of the young age of this patient group, even impairments of mild severity can potentially affect performance in the school or work environment and thus represent a detrimental postacute outcome. Furthermore, our findings show that standardized cognitive testing is essential to assess outcome in the postacute phase of patients with NMDAR encephalitis. Therefore, cognitive measures should also be included in clinical studies in addition to measures of functional neurological outcome.

Core Cognitive Deficits: Memory Impairment and Executive Dysfunction

Our data illustrate that the cognitive profile of NMDAR encephalitis in adults is characterized by deficits of verbal episodic memory, working memory, and executive function. This predominant mnestic–executive presentation corresponds with the distribution of NMDARs, with highest receptor densities in the hippocampus (cornu ammonis 1 region and dentate gyrus) and the frontal cortex (cortical layers I–III).[28,29] NMDARs regulate synaptic transmission and plasticity[30] involved in long-term potentiation[31] and long-term depression[32] during memory encoding and consolidation. Memory impairment and executive dysfunction are, therefore, likely consequences of frontal and medial temporal NMDAR dysfunction. In line with this hypothesis, decoupling of the hippocampus and the medial prefrontal cortex correlates with severity of memory deficits in NMDAR encephalitis patients.[11] At the same time, structural hippocampal damage (ie, reduced hippocampal volume and decreased microstructural integrity)[33] is associated with memory impairment. Dysfunction of NMDARs in the frontal cortex is a likely correlate of the frequent impairment of executive function. Indeed, administration of the NMDAR antagonist ketamine not only causes memory deficits,[34] but also leads to increased error rates and stronger perseverance in the Wisconsin Card Sorting Test,[35] a standard test of executive function. In addition, extensive white matter damage[11,36,37] and whole-brain functional connectivity changes[11,38] contribute to cognitive deficits beyond memory and executive dysfunction. Interestingly, the cognitive deficit profile of NMDAR encephalitis seems to be different in children, where predominant impairment of sustained attention was observed.[26]

Predictors for Long-Term Cognitive Outcome

Our regression analyses showed that delayed immunotherapy and higher disease severity during the acute phase are predictors of impaired long-term cognitive outcome. Specifically, patients with delayed treatment start had more severe deficits of verbal memory and executive function, ie cognitive processes related to inhibitory and attentional control, mental flexibility, problem solving, and action planning. These results highlight the need to provide a rapid diagnostic workup and treatment of patients with NMDAR encephalitis, as a failure to do so can cause a significant negative impact on academic achievement and social interaction of patients. In addition, impaired

working memory and visual memory outcome were predicted by higher disease severity, assessed as need for longer hospitalization, need for ICU treatment, and higher acute phase mRS. These findings corroborate previous exploratory observations in a small cross-sectional study on cognitive outcome in NMDAR encephalitis.[3] Furthermore, our results are in line with findings from large-cohort studies that identified later treatment and more severe disease symptoms (assessed as need for ICU treatment) as predictors of general disability (mRS).[1,39] Overall, the identified clinical predictors can help to guide clinical management decisions to achieve good cognitive long-term outcomes and prevent long-term impairments in the core cognitive deficit domains of NMDAR encephalitis, ie memory and executive function.

Long-Term Recovery of Cognitive Function

The temporal dynamics of cognitive recovery show greater gains earlier in the postacute phase, with continued improvement of cognitive function even several years after disease onset in some patients. Despite noticeable subjective memory and concentration complaints at first study visit, many patients reported subjective cognitive improvement or stable abilities at second study visit. In correlation analyses, we observed that greater improvement occurs in the early recovery phase. Nonetheless, our analysis showed that recovery can continue for years, with improvements in working memory, verbal episodic memory, and attentional performance. These results can help to counsel patients and relatives that improvement of cognitive function is time specific and can continue for several years. Vice versa, these data can be used to estimate the temporal boundaries of the recovery period and suggest a time point at which cognitive deficits can be considered persistent. Furthermore, our results highlight that current cognitive rehabilitation approaches may be insufficient for most patients, given their typical limitation to several weeks or at most a few months, calling for longer and individually adapted rehabilitation regimens.

Implications for Clinical Management

Our results have several implications for the clinical management of patients with NMDAR encephalitis: (1) all patients should receive dedicated neuropsychological testing after the acute disease stage, and clinical studies should include cognitive performance as outcome measures; (2) the high risk for cognitive long-term deficits should be considered in the decision-making process for the initiation and escalation of immunotherapy, as late treatment and severe disease symptoms are associated with worse cognitive outcome; (3) patients and relatives should be counseled about the risk for cognitive long-term impairments, but also about the potential for continued recovery for several years; and (4) finally, our results call for continued and dedicated cognitive rehabilitation in patients with NMDAR encephalitis to support the observed recovery process over several years. Targeting mnemonic and executive function—ideally in individually tailored cognitive interventions[8]—may be particularly helpful to achieve a favorable long-term outcome. In a study of pediatric NMDAR encephalitis, attention deficits and fatigue had a persisting impact on school performance, so that one third of the children did not return to their previous school level.[26] Ameliorating the impact of autoimmune encephalitis on cognitive performance should therefore be one of the main treatment goals to preserve long-term educational and occupational potential in these patients.

Contrary to our expectations, we did not observe better functional neurological and cognitive outcomes in patients with a more recent disease onset, although this observation cannot be generalized to other clinical settings and institutions. Nevertheless, we expect that the increasing awareness of NMDAR encephalitis and consequently shorter treatment delays together with a broadening treatment spectrum and earlier application of second-line immunotherapies will lead to better long-term cognitive outcomes in future NMDAR encephalitis patients.

Limitations

Patients were prospectively enrolled in this study without restrictions regarding the time since disease onset and first study visit. Although this allowed us to analyze later stages of the recovery process, it also resulted in considerable variability for the time between disease onset and first study visit. For instance, although most patients were enrolled about 1 to 3 years after their disease onset (median = 2.3 years), there were single patients with earlier and later enrollment (range = 0.3–7.0 years). Importantly, this variability was statistically accounted for using linear mixed effects analyses and study visits were unrelated to other medical consultations. Nevertheless, this limitation should be addressed in future prospective studies with testing of patients at regularly timed study visits.

The current study included all patients irrespective of ongoing symptoms, that is, both patients with (73%) and without (27%) subjective cognitive symptoms, ie our rates of neuropsychological deficits are comparable to those reported in a recent systematic review.[2] The good functional neurological outcomes of patients in our study (in contrast to persistent cognitive impairment) also speak against a selection bias toward inclusion of more severely affected cases. However, to fully exclude selection biases,

future studies should aim to study all patients in a predefined region and time.

Neuropsychological testing is often difficult to perform during the acute phase of the disease (due to severe symptoms, decreased levels of consciousness, or drug effects), when cognitive symptoms are most pronounced. Comprehensive assessments, such as in this study, are therefore limited to the recovery phase after the peak of the disease. There are, nonetheless, several case studies that describe cognition in severely impaired patients using individually adapted neuropsychological protocols.[40–42] Although we controlled the impact of practice effects at second study visits using parallel versions or randomization of trials wherever applicable, we cannot fully exclude the impact of familiarity with the task design.

Conclusions

In conclusion, this study presents comprehensive longitudinal data for the cognitive outcome in NMDAR encephalitis. All patients had cognitive deficits approximately 2 years after disease onset, mainly affecting memory and executive function. After almost 5 years, moderate or severe cognitive deficits persisted in two thirds of patients despite good functional neurological outcome, indicating that cognitive function is an important outcome measure in addition to the functional neurological scales. Impaired cognitive outcome was predicted by delayed treatment and higher disease severity. However, continued improvement of cognitive function was observed for several years after disease onset in some patients. Our results demonstrate that cognitive deficits are frequent and severe long-term sequelae following NMDAR encephalitis. These deficits show a slow and incomplete recovery and persist beyond recovery of other neuropsychiatric symptoms of the disease. Consequently, our findings call for rapid diagnosis and treatment at disease onset as well as for continued and customized cognitive rehabilitation to improve the long-term outcome.

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Author Contributions

J.H., U.A.K., and C.F. conceived and designed the study. J.H., U.A.K., J.K., H.P., and C.F. acquired and analyzed the data. J.H., C.J.P., and C.F. drafted the manuscript and figures.

Potential Conflicts of Interest

Nothing to report.

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