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REVIEW ARTICLE

Cognitive outcomes following anti-N-methyl-D-aspartate receptor encephalitis: A systematic review

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ABSTRACT

Introduction: Anti-N-methyl-D-aspartate receptor (NMDAR) encephalitis is an immune-mediated neurological disorder that (among other severe neuropsychiatric symptoms) affects cognition. This study aimed to summarize current knowledge regarding the rates, nature, and predictors of neuropsychological dysfunction in patients recovering from anti-NMDAR encephalitis. *Method*: A systematic review of studies describing neuropsychological outcomes following anti-NMDAR encephalitis was conducted. Electronic databases Medline, PsycINFO, EMBASE, and CINAHL were searched from inception to September 2016. Results were summarized using descriptive statistics and a series of chi-square analyses. *Results*: Of 4030 identified studies, 44 were included. These reported neuropsychological outcomes for 109 treated patients (83.5% female, M_{age} = 22.5 years, range = 2–67) recovering from anti-NMDAR encephalitis. High rates of neuropsychological dysfunction were identified, with diverse impairments of variable severity documented in >75% of patients at assessments conducted during acute, subacute, and longer term recovery periods. Despite this, cognitive outcomes were ultimately considered favorable in most cases (74.3%). This estimate does not account for the potential impact of relapses. The frequency of impairments in overall intellectual functioning, language, attention, working memory, and visuospatial functions were significantly higher within the acute recovery period than in later phases of convalescence. However, rates of impaired processing speed, episodic memory, and aspects of executive functioning were consistent across time points. Adverse neuropsychological outcomes occurred at significantly higher frequency in patients where immunotherapy was delayed, $\chi^2(1, N = 66) = 10.84$, $p < .003$. *Conclusions*: Neuropsychological deficits are prevalent at all points of recovery from anti-NMDAR encephalitis, although improvement in cognitive outcomes can be expected as patients recover. Some cognitive deficits may be less likely than others to resolve. Close neuropsychological monitoring is warranted in this population. Longitudinal studies of neuropsychological functioning of patients with anti-NMDAR encephalitis are needed to accurately inform prognosis.

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Anti-N-methyl-D-aspartate receptor encephalitis; autoimmune diseases; cognitive disorders; neuropsychological tests; treatment outcome

First characterized in 2007, anti-N-methyl-D-aspartate receptor (NMDAR) encephalitis is a severe but treatable autoimmune disorder associated with a characteristic, multistage neuropsychiatric syndrome (Dalmau et al., 2008; Dalmau, Lancaster, Martinez-Hernandez, Rosenfeld, & Balice-Gordon, 2011; Dalmau et al., 2007). The disorder usually presents with nonspecific prodromal symptoms, followed by acute-onset behavioral and mental state disturbance. The syndrome subsequently progresses to include seizures, dyskinesias, language disintegration, decreased consciousness, catatonia, and autonomic dysfunction. Patients are often left with neuropsychological sequelae (Finke et al., 2012; McKeon et al., 2016). This systematic review aims to explore this aspect of recovery.

Although the incidence of anti-NMDAR encephalitis is unknown (Dalmau et al., 2011), the disorder is considered the leading cause of encephalitis in people below the age of 30 (Gable, Sheriff, Dalmau, Tilley, & Glaser, 2012). Approximately 81% of patients with

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Supplemental data for this article can be accessed here.

anti-NMDAR encephalitis are young females of reproductive age (median = 21 years; range = 8 months to 85 years; Titulaer et al., 2013), although males and older adults can also be affected (Dalmau et al., 2011; Dalmau & Rosenfeld, 2014). The syndrome is paraneoplastic (usually ovarian teratomas) in approximately 45% of adult cases, although underlying neoplasms are less common in males, children, and patients of advanced age (Dalmau et al., 2011).

The symptoms and progression of the syndrome can be attributed to the pathogenic effects of antibodies upon the usual functioning of the NMDAR system (Dalmau et al., 2008; Hughes et al., 2010; Moscato et al., 2014). The ubiquitously expressed NMDARs are one of three receptor families responsible for mediating synaptic transmission of the amino acid glutamate, which is the primary excitatory neurotransmitter in the mammalian central nervous system (CNS; Kalia, Kalia, & Salter, 2008; Molnar, 2008; Paoletti & Neyton, 2007). Of note for memory and learning, the hippocampus contains the highest density of NMDARs, which are important for shaping the strength of synaptic connections through their involvement in long-term potentiation (LTP) and the opposing process of long-term depression (LTD; Molnar, 2008; Newcomer & Krystal, 2001; Waxman & Lynch, 2005). In anti-NMDAR encephalitis, patient antibodies effectively eliminate NMDAR-associated synaptic functions by targeting the NR1 receptor subunit and causing a selective, reversible decrease in NMDAR surface density, synaptic localization, and currents (Dalmau et al., 2008; Hughes et al., 2010; Moscato et al., 2014).

Despite evidence that immunotherapy and tumor removal (where indicated) result in favorable clinical outcomes for the majority of patients (81%; Titulaer et al., 2013), recent neuropsychological research suggests that cognitive impairments constitute a major morbidity of the disorder (Finke et al., 2012; McKeon et al., 2016). Specifically, persistent cognitive deficits consistent with diminished NMDAR functioning have been reported up to several years post clinical remission, predominantly in the domains of executive functioning and memory (Finke et al., 2012; McKeon et al., 2016). Emerging evidence has highlighted the relevance of structural and functional neurological changes (particularly hippocampal) to performance on memory testing following anti-NMDAR encephalitis (Finke et al., 2013, 2016). Consistent with clinical outcomes research (Titulaer et al., 2013), Finke et al. (2012) demonstrated that poorer cognitive outcomes were related to delayed treatment, but not higher initial antibody levels. Other predictors of poorer clinical outcomes include nonparaneoplastic syndromes (Dalmau et al., 2008, 2011; Florance et al., 2009) and intensive care unit (ICU) admissions (Titulaer et al., 2013).

However, other as yet unexplored factors may be related to neuropsychological outcomes in this population. Given developmental changes in NMDAR expression (Haberny et al., 2002; Molnar, 2008), hypofunction of this system during critical periods such as childhood and adolescence may affect normal CNS function more so than adult-onset episodes. Similarly, as males may be more susceptible to the effects of NMDAR antagonism than females (Morgan, Perry, Cho, Krystal, & D'Souza, 2006), sex is potentially relevant to cognitive outcomes following anti-NMDAR encephalitis. Severe seizure activity may also be associated with poorer cognitive outcomes in these patients (Avanzini, Depaulis, Tassinari, & de Curtis, 2013).

Although there are case reports and a small number of case series with modest sample sizes (Finke et al., 2012; McKeon et al., 2016) describing cognitive functioning in patients recovering from anti-NMDAR encephalitis, these have not been systematically examined. Collating this data could both inform the understanding of cognitive functioning following anti-NMDAR encephalitis and identify prognostic factors associated with future neuropsychological functioning.

Correspondingly, this systematic review aims to identify studies reporting neuropsychological outcomes following anti-NMDAR encephalitis. This study seeks to: (a) summarize findings according to major neuropsychological domains assessed and stage of recovery; (b) investigate potential relationships between acute illness clinical variables and subsequent neuropsychological outcomes; and (c) make recommendations for neuropsychological assessments with this population. It is expected that the compilation of an up-to-date summary of neuropsychological outcomes relevant to this syndrome could lead to more expeditious identification of residual cognitive impairments. In turn, this could inform rehabilitation and improve prognosis.

Method

A systematic literature review was conducted in accordance with the guidelines proposed by the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) group (Moher, Liberati, Tetzlaff, & Altman, 2009). The Medline, PsycINFO, EMBASE, and CINAHL databases were searched from their inception years to September 2016. The search strategy was structured to capture all studies describing cognitive outcomes following treatment for anti-NMDAR encephalitis. The search string (see Figure 1) was applied to titles and abstracts. Additionally, articles

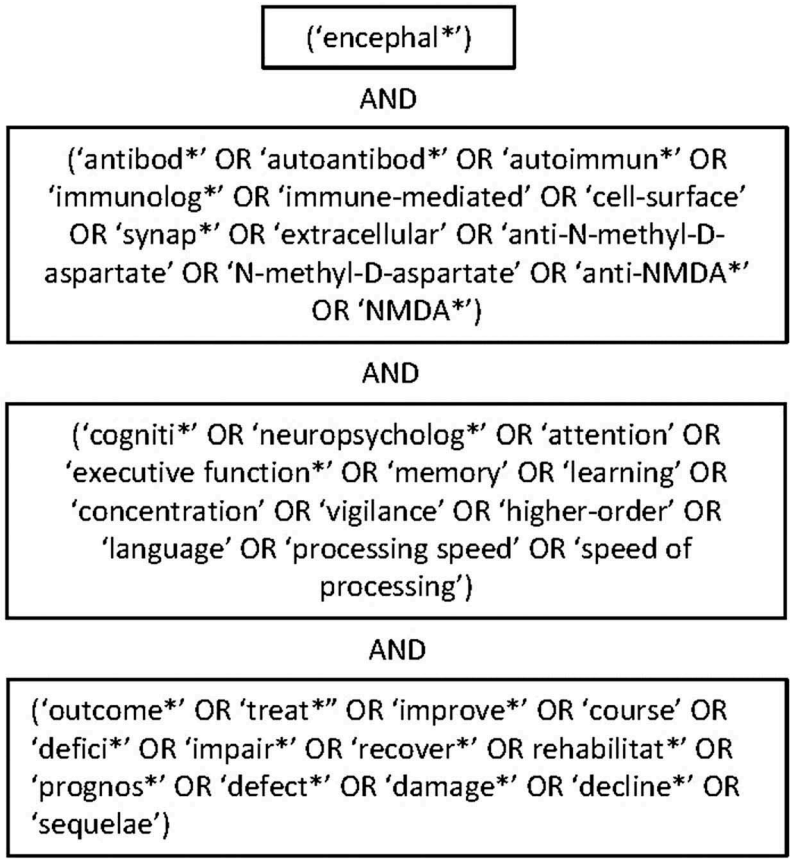

Figure 1. Search strategy.

were sourced that were referenced in Medline and EMBASE under the Medical Subject Heading term "Anti-N-Methyl-D-Aspartate Receptor Encephalitis."

Reference lists of relevant papers were searched to identify additional studies not captured by the search strategy. Where relevant secondary sources such as reviews or meta-analyses were identified, primary articles were obtained. There were no limitations applied to the language of publication. Full-text versions of potentially relevant non-English language articles were translated and also read in full. Potentially relevant articles were reviewed in full by one of the authors (G.M.). Where uncertainties emerged, these references were independently reviewed by another author (A.R.), with final decisions reached through discussion and consensus.

Study inclusion/exclusion criteria

Eligible studies fulfilled the following criteria:

(1) *Anti-NMDAR encephalitis diagnosis*. Studies reported a patient sample diagnosed with anti-NMDAR encephalitis, as confirmed through cerebrospinal fluid (CSF) and/or serum analyses. Patients with comorbid neurological disorders or premorbid intellectual disability were excluded.

(2) *NMDAR antibodies*. Included cases were restricted to patients with clinically elevated CSF and/or serum levels of NMDAR antibodies. Patients with additional antibodies targeting extracellular, intracellular, or undefined antigens were excluded.

(3) *Neuropsychological testing*. Evidence of formal neuropsychological assessment was required (see supplementary Figure S1 for further detail). Studies were omitted where there was inadequate information to determine that further testing was undertaken beyond screening instruments such as the Mini Mental State Examination.

(4) *Assessment following treatment*. Measures were administered during the convalescence period. Specifically, patients must have received treatment for anti-NMDAR encephalitis.

(5) *Description of outcomes*. Eligible studies reported neuropsychological outcomes in

enough detail to infer whether performance was impaired or spared. Studies reliant on clinician or caregiver ratings of clinical or functional outcomes through measures such as the Modified Rankin Scale were excluded. Accepted methods for reporting outcomes can be viewed in supplementary Figure S1.

Data extraction

Where reported, the following data were extracted from eligible studies: (a) study identifiers and descriptors (authors, year, country of origin); (b) patient demographics (age, sex); (c) acute illness clinical variables (disease etiology; magnetic resonance imaging/electroencephalography, MRI/EEG, findings; presence/absence of seizures; evidence of particularly severe illness, e.g., ICU stay or life-threatening autonomic instability); (d) nature of treatment and estimated untreated duration; (e) testing characteristics (names of measures, deficit definitions, time elapsed between treatment initiation, and test administration); and (f) key findings regarding neuropsychological outcomes and any comments on functional status. Where the timing of assessments in relation to treatment initiation was able to be determined, evaluations were classified as occurring within the acute, subacute, or longer term phases of recovery. These periods were defined as assessments administered within 3, between 3 and 12, and >12 months after initial administration of immunotherapy, respectively.

For the purposes of exploring the nature and course of neuropsychological dysfunction in patients recovering from anti-NMDAR encephalitis, the results of all assessments were categorized into eight broad cognitive domains, including overall intellectual ability, memory, language, executive functioning, working memory, attention, visual–spatial cognition, and information processing speed. Classification of measures within domains was guided by conventional neuropsychological practice methods (Lezak, Howieson, Bigler, & Tranel, 2012; Strauss, Sherman, & Spreen, 2006).

There was no consensus within the anti-NMDAR encephalitis literature with respect to the circumstances under which neuropsychological outcomes should be considered adverse or more favorable. The current reviewers developed a set of basic criteria to classify adverse anti-NMDAR encephalitis neuropsychological outcomes, with a view to facilitating an exploratory analysis of potentially relevant prognostic factors. Our criteria were formulated on the basis of direct clinical experience and review of the anti-NMDAR encephalitis literature. Accepted approaches to the identification of cognitive impairment in patients with a more common autoimmune neurological disorder (multiple sclerosis) were also considered (Fischer et al., 2014).

Adverse cognitive outcomes were recorded where there was evidence of: (a) impairment in overall level of cognitive functioning; (b) neuropsychological deficits accompanied by evidence of a deterioration in functioning from premorbid status; or (c) pervasive neuropsychological deficits defined as impairments in ≥4 cognitive domains. Where patients were assessed on multiple occasions, and none of these criteria were met by the final point of follow-up, an adverse outcome was only recorded if testing performance had declined significantly (i.e., ≥1 *SD*) in any domain.

Statistical analyses

Major findings regarding cognitive outcomes were collated and tabulated. Data were descriptively summarized according to rates of impairments within neuropsychological domains and the timing of the assessment in relation to treatment initiation. Meta-analysis was not considered appropriate given the notable heterogeneity evident across studies with respect to variables such as assessments administered, length of treatment, and thresholds used to define cognitive impairments. However, an exploratory series of chi-square tests were utilized to investigate: (a) how the frequency of specific neuropsychological deficits might vary according to the period of recovery at which the patient is assessed; and (b) whether clinical/demographic variables were associated with posttreatment neuropsychological outcomes. Where a significant association was evident ($\alpha < .05$), odds ratios were calculated with 95% confidence intervals.

Results

Included studies

The search strategy yielded 7902 potentially relevant citations, which were imported or manually entered into an Endnote X7 database. Once duplicates were removed, 4030 titles and abstracts underwent screening for relevance. Full-text versions of 975 potentially eligible studies were acquired and read in full. Forty-four studies met inclusion criteria (Figure 2). Included studies originated from a broad spectrum of 16 internationally representative countries. Nine years of research were covered, with studies published between 2008 and 2016.

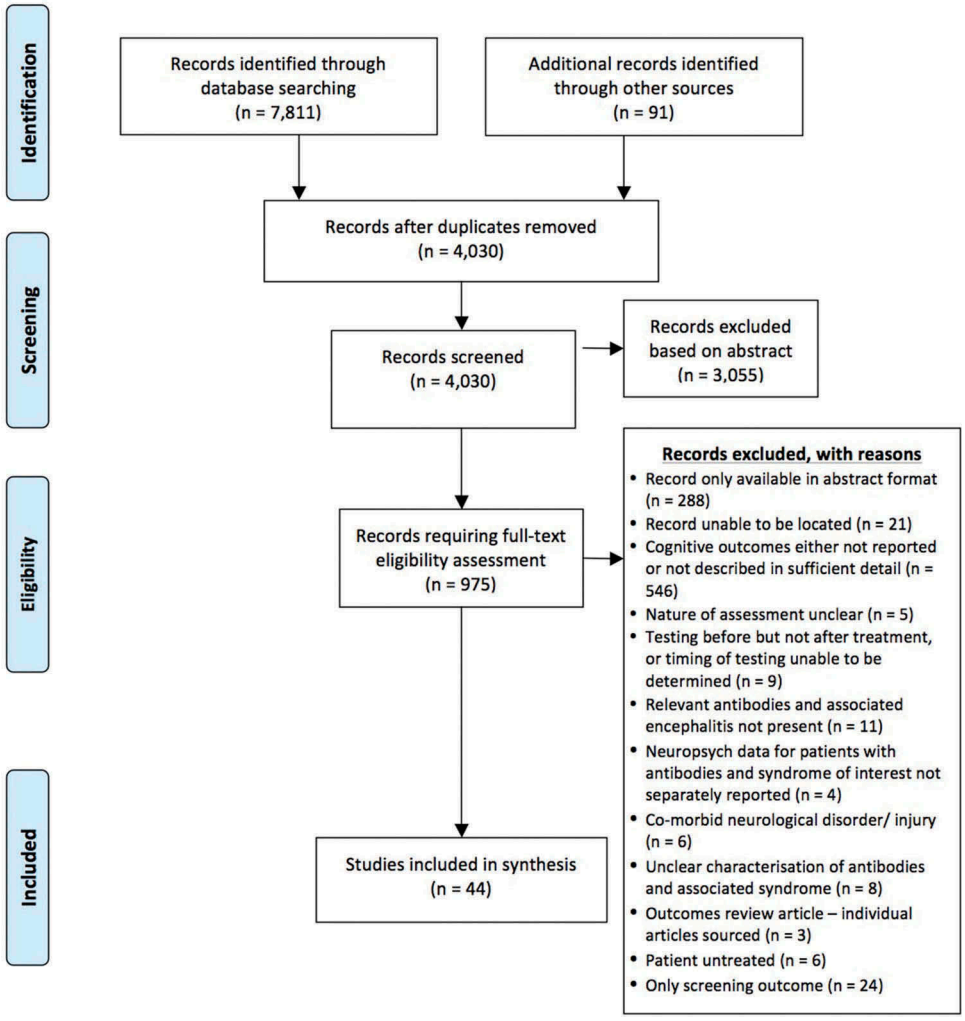

Figure 2. PRISMA flowchart.

Patient information

Neuropsychological outcomes were reported for 109 patients treated for anti-NMDAR encephalitis (M_{age} = 22.5 years, range = 2–67 years, 83.5% female). MRI results were described for 105 cases, which were abnormal in 41.9%. Affected regions are illustrated in Figure 3. The frequencies of all relevant acute illness clinical/demographic variables are summarized in Table 1. Clinical data relevant to individual patients are provided within online supplementary material.

Neuropsychological testing

Results of 149 neuropsychological assessments were reported in relation to the 109 included patients. Neuropsychological tests were specified in 132 instances (88.6%), with the remaining 17 assessments (11.4%) documenting the results of "neuropsychological" evaluations without naming the measures administered. Twenty-seven patients (28.7%) were assessed on more than one occasion. It could be determined that assessments were administered in relation to treatment initiation as follows: 30 within the acute, 38 in the subacute, and 58 evaluations in the longer term phases of recovery. Specified assessment timepoints ranged from immediately post treatment (i.e., within 24 hours) up to nine years post onset of encephalitis. The timing of neuropsychological assessment in relation to treatment initiation was unable to be determined in 23 instances.

Studies assessed a variety of cognitive domains, including: premorbid intelligence (n = 5), overall intellectual functioning (n = 19), visual–spatial abilities (n = 25), language (n = 28), memory (n = 24), working memory (n = 21), attention (n = 20), processing speed (n = 20), executive functioning (n = 23), and social cognition (n = 2). Performance thresholds representing impairment were explicitly defined in relation to 84 (56.4%) assessments. Data of variable quality were

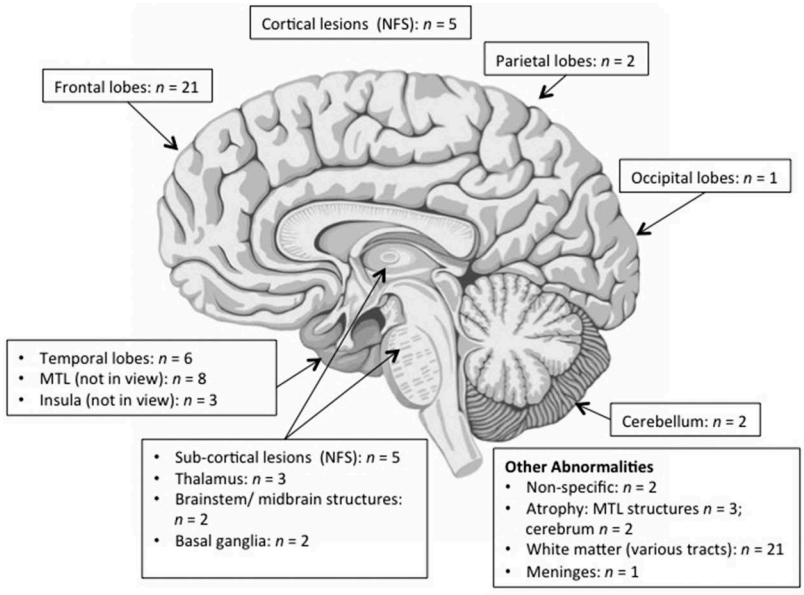

Figure 3. Distribution of abnormal acute illness cerebral magnetic resonance imaging (MRI) results. MTL = medial temporal lobe.

Table 1. Frequency of acute illness clinical variables.

Variables	*n* (%)
Abnormal MRI	44/105 (41.9)
Abnormal EEG	54/58 (93.1)
Seizures	82/109 (75.2)
Evidence of life threatening syndrome	32/69 (46.4)
Delayed treatment	13/66 (19.7)
2nd line immunotherapy administered	28/109 (25.7)
Paraneoplastic syndrome	22/108 (20.4)
Child or adolescent	38/109 (34.9)
Female gender	91/109 (83.5)

Note. MRI = magnetic resonance imaging; EEG = electroencephalography.

provided in enough detail to infer whether deficits had been interpreted in line with accepted clinical neuropsychological practice methodology in 93 out of 149 assessments (62.4%). Although a universal definition of neuropsychological deficit does not exist, the current study utilized a conventional threshold (<9th percentile; Brooks, Sherman, Strauss, Iverson, & Slick, 2009; Lezak et al., 2012) to infer impairments where data were provided. In 21 assessments (14.1%) unambiguous descriptions of neuropsychological outcomes were provided without definition of deficit thresholds or presenting data. Supplementary Table 2 presents a complete summary of information relevant to neuropsychological assessments administered to patients.

Neuropsychological functioning throughout recovery

The frequency of specific neuropsychological deficits at various points of recovery are summarized in Table 2 and are illustrated visually in Figure 4. Table 3 presents the results of chi-square analyses examining the significance of relationships between assessment timing and prevalence of neuropsychological deficits. The rates of cognitive deficits identified at three separate cross-sectional time points were comparably high (>75%). The prevalence of patients identified with impairments in overall intellectual functioning, language, attention, working memory, and visual–spatial cognition varied according to assessment timing, with significantly higher rates of dysfunction apparent at earlier points of recovery. Rates of performance impairments on tests of executive functioning, episodic memory, and processing speed were unrelated to assessment timing. Although not analyzed within the remit of a major domain of cognition, it is worth noting that two studies (Bach, 2014; McKeon et al., 2016) reported evidence of social cognition deficits in eight patients recovering from anti-NMDAR encephalitis after variable lengths of follow-up. Objective measures of social cognition were only administered in one of these studies (McKeon et al., 2016).

Table 2. Summary of neuropsychological outcomes in patients recovering from anti-NMDAR encephalitis.

			Cognitive domain[a]									
Reference	ID	Time point	IQ	Mem	Lang	Attn	WM	EF	VS	IPSp	Cognitive outcome	Outcome rationale
Asai, Morinaga, Yamamoto, and Imamura (2014)	P1	2		✗	✗	✗	✗	✗	✗	✗	+	Performance improved. Focal deficit. No evidence of functional impact.
		3	✓		✗	✓	✓		✓	✓		
Bach (2014)	P2	NQ		✗	✗	✗	✗	✗	✓	✗	–	Extensive deficits. Functional impact.
	P3	NQ		✓	✓	✓	✗	✗	✓	✗	+	Functioning improved. Relatively focal deficits.
Berg, Byrne, and Coffey et al. (2015)	P4	NQ	✗								–	Intellectual sequelae.
Bowes et al. (2015)	P5	1	✓	✗	✗		✗	✗		✗	–	Extensive deficits.
Bradley (2015)	P6	1		✓		✓		✗			+	Functioning improved. Focal deficit.
Brier, Day, Snyder, Tanenbaum, and Ances (2016)	P7	2		✗	✗			✗		✗	+	Performance improved. Relatively focal deficits.
		3		✗	✓			✗		✗		
Consoli et al. (2011)	P8	1		✗	✓	✗	✗		✗	✗	+	Performance improved. No deficits.
		2	✓		✓	✓	✓		✓	✓		
		2	✓	✗	✓	✓	✗		✓	✓		
		3		✓	✓		✓		✓			
Dericioglu et al. (2013)	P9	3									+	No deficits.
Dogan Onugoren et al. (2016)	P10	NQ		✗							+	Performance improved. No deficits. No evidence of functional impact.
		NQ		✓								
		NQ		✓								
	P11	1		✓							+	No deficits. No evidence of functional impact.
		1		✓								
		2		✓								
	P12	1		✗							–	Persistent deficits. No evidence of functional impact.
		1		✗								
		2		✗								
	P13	1		✗							+	Performance improved. No deficits. No evidence of functional impact.
		1		✓								
		2		✓								
	P14	3		✗							–	Persistent deficits. Functional impact.
		3		✗								
		3		✗								
	P15	1		✗							–	Performance deficit. Functional impact.
	P16	NQ		✓							–	Performance fluctuated. Evidence of functional impact.
		NQ		✗								
		NQ		✓								
Eker et al. (2008)	P17	1		✓	✓	✓	✓	✓	✓	✓	+	No deficits.
Finke et al. (2012)	P18	3	✓	✗	✓	✗	✗	✗	✓	✗	–	Extensive deficits.
	P19	3	✓	✓	✓	✗	✓	✓	✓	✓	+	Focal deficit.
	P20	3	✓	✓	✓	✓	✓	✗	✓	✓	+	Focal deficit.
	P21	3	✓	✓	✓	✓	✓	✓	✓	✓	+	No deficits.
	P22	3	✓	✗	✓	✓	✓	✓	✓	✓	+	Focal deficit.
	P23	3	✓	✗	✓	✗	✓	✓	✓	✓	+	Relatively focal deficits.
	P24	3	✓	✓		✗	✓	✗	✓	✗	+	Relatively focal deficits.
	P25	3	✓	✗	✗	✓	✗	✗	✓	✓	–	Extensive deficits.
Finke et al. (2013)	P26	3	✗	✗	✗	✗	✗	✗	✗		–	Extensive deficits. Functional impact.
	P27	3	✓	✗	✓	✗	✓	✗	✓		+	Relatively focal deficits. Minimal functional impact.
	P28	NQ	✓	✓	✓	✓	✓	✓	✓		+	No deficits. No evidence of functional impact.
	P29	3	✓	✓	✓	✓	✓	✓	✓		+	No deficits. No evidence of functional impact.

(*Continued*)

Table 2. (Continued).

Reference	ID	Time point	Cognitive domain[a]								Cognitive outcome	Outcome rationale
			IQ	Mem	Lang	Attn	WM	EF	VS	IPSp		
	P30	3	✓	✓	✓	✗	✓	✗	✓		+	Relatively focal deficits. Minimal functional impact.
	P31	NQ	✓	✓	✓	✓	✗	✓	✓		+	Relatively focal deficits. Minimal functional impact.
	P32	3	✓	✓	✓	✓	✓	✓	✓		+	No deficits. No evidence of functional impact.
	P33	3	✓	✓	✓	✓	✓	✓	✓		+	No deficits. No evidence of functional impact.
	P34	3	✓	✓	✓	✗	✗	✓	✓		+	Relatively focal deficits. Minimal functional impact.
	P35	NQ	✓	✓	✓	✗	✓	✓	✓		+	Relatively focal deficits. Minimal functional impact.
	P36	3	✓	✗	✓	✓	✓	✓	✓		+	Relatively focal deficits. Minimal functional impact.
	P37	NQ	✓	✗	✓	✓	✓	✓	✓		+	Relatively focal deficits. Minimal functional impact.
	P38	NQ	✓	✗	✓	✗	✗	✗	✓		−	Extensive deficits. Functional impact.
	P39	NQ	✓	✓	✓	✓	✓	✗	✓		+	Relatively focal deficits. Minimal functional impact.
	P40	3	✓	✗	✓	✓	✗	✓	✓		+	Relatively focal deficits. Minimal functional impact.
	P41	NQ	✓	✗	✓	✗	✗	✓	✓		+	Relatively focal deficits. Minimal functional impact.
	P42	3	✓	✗	✓	✓	✓	✓	✓		+	Focal deficit. Minimal functional impact.
Finke et al. (2016)	P43	NQ		✗	✗	✗	✗	✗	✓		−	Extensive deficits.
	P44	2		✓	✓	✗	✗	✓	✓		+	Relatively focal deficits.
	P45	3		✗	✓	✗	✗	✗	✓		−	Extensive deficits.
	P46	2		✗	✓	✓	✗	✓	✓		+	Relatively focal deficits.
	P47	1		✓	✓	✓	✓	✓	✓		+	No deficits.
	P48	2		✓	✓	✓	✓	✓	✓		+	No deficits.
	P49	NQ		✗	✓	✓	✗	✓	✓		+	Relatively focal deficits.
	P50	NQ		✓	✓	✓	✗	✓	✓		+	Focal deficit.
	P51	NQ		✗	✓	✓	✓	✓	✓		+	Focal deficit.
	P52	3		✗	✓	✗	✗	✗	✓		−	Extensive deficits.
	P53	2		✗	✓	✓	✗	✓	✓		+	Relatively focal deficits.
	P54	NQ		✓	✓	✓	✓	✓	✓		+	No deficits.
	P55	3		✓	✓	✗	✗	✓	✓		+	Relatively focal deficits.
	P56	3		✓	✓	✗	✓	✓	✓		+	Focal deficit.
	P57	3		✗	✓	✓	✓	✓	✓		+	Focal deficit.
Freri et al. (2015)	P58	2	✓		✗		✓		✓	✓	+	Focal deficit.
Gataullina et al. (2011)	P59	2			✗						+	Focal deficit.
Gonzalez-Latapi, Rodriguez-Violante, Cervantes-Arriaga, Celleja-Castillo, and Gonzalez-Aguilar (2014)	P60	2		✗		✗					+	Relatively focal deficits.
Guo et al. (2014)	P61	3	✗		✗				✗		−	Intellectual sequelae.
		3	✗		✗				✗			
Hinkle et al. (2016)	P62	1	✓	✗	✗	✓	✓	✗	✗	✓	+	Performance improved. Relatively focal deficits. No evidence of functional impact.
		2		✗	✗	✓		✗	✓	✓		
		1									+	Relatively focal deficits. No evidence of functional impact.
	P63	2	✓	✓	✓	✓	✓	✗	✓	✗		
	P64	1		✗	✗	✗	✗	✗	✗	✗	+	Performance improved. No evidence of functional impact. "Mild declines" attributed to test-taking behavior. Language difficulties reported premorbidly.
		2	✓	✗	✗	✓	✓	✓	✗	✗		
		3	✓	✓	✗	✓	✓	✗	✗	✗		
Hole, Lennon, Cohen, and Sokol (2014)	P65	2			✗				✗		−	Intellectual sequelae.
Huang et al. (2015)	P66	2	✓	✗	✓	✓	✓	✓	✓	✓	+	Focal deficit.
Iadisernia et al. (2012)	P67	2	✗	✓	✗	✗		✗	✓		+	Intellectual sequelae that later normalized.

(*Continued*)

Table 2. (Continued).

Reference	ID	Time point	Cognitive domain[a]								Cognitive outcome	Outcome rationale
			IQ	Mem	Lang	Attn	WM	EF	VS	IPSp		
	P68	3	✗	✓	✗	✗		✗	✗		–	Intellectual sequelae.
Jantzen et al. (2013)	P69	2		✗	✓	✓	✓	✓		✓	+	Focal deficit. No evidence of functional impact.
Kashyape et al. (2012)	P70	2									+	No deficits.
Kuroda et al. (2015)	P71	2	✓	✓	✓	✓	✓	✓	✓	✓	+	No deficits.
Le Foll and Pelletier (2010)	P72	2		✗			✗				+	Relatively focal deficits.
Lebon et al. (2012)	P73	2	✓		✓	✓	✓		✓	✗	+	Focal deficit. No evidence of functional impact.
Loughan, Allen, Perna, and Malkin (2016)	P74	2	✓	✓	✗	✓	✓	✗	✓	✗	+	Relatively focal deficits. Minimal functional impact.
Marcos-Arribas, Jimenez Almonacid, and Dolado (2013)	P75	1		✓	✓	✓	✗	✓	✓	✓	+	Focal deficit. Minimal functional impact.
Martinez, Guerrero, Grandjean, and Cartier (2012)	P76	1		✗	✗	✗		✗	✗		–	Extensive deficits. Evidence of functional impact.
Martin-Monzon et al. (2012)	P77	NQ	✗	✗	✗	✗	✗	✗	✗	✗	+	Performance improved. No deficits.
		2	✗	✗	✓	✗	✓	✗	✗	✓		
		3	✓	✓	✓	✓	✓	✓	✓	✓		
Matricardi et al. (2016)	P78	1	✓		✗	✗	✓	✓	✓	✓	+	Focal deficit. Performance improved. No evidence of functional impact.
		3	✓		✗	✓	✓	✓	✓	✓		
	P79	1	✓		✗	✗	✓	✓	✓	✗	+	Relatively focal deficits. No evidence of functional impact.
	P80	1	✗		✗	✗	✗	✗	✗	✗	+	Relatively focal deficits. Performance improved. No evidence of functional impact.
		3	✓		✗	✓	✓	✓	✗	✓		
	P81	1	✗		✗	✗	✗	✗	✗	✗	+	Relatively focal deficits. Performance improved. No evidence of functional impact.
		3	✓		✓	✓	✓	✗	✗	✗		
	P82	1	✗		✗	✗	✗	✗	✗	✗	–	Extensive impairments. Intellectual sequelae.
	P83	1	✗		✗	✗	✗	✗	✗	✗	+	Relatively focal deficits. Performance improved. No evidence of functional impact.
		2	✓		✓	✓	✓	✓	✗	✗		
	P84	1	✗		✗				✗		+	Performance improved. No deficits. No evidence of functional impact.
		2	✓		✓				✓	✓		
	P85	2	✓		✓	✗		✗	✗		–	Relatively focal deficits. Evidence of clinically significant deterioration in attention domain.
		3	✓		✓	✗	✓	✓	✗	✗		
	P86	2	✓		✗	✗			✗	✓	+	Performance improved. No deficits. No evidence of functional impact.
		3	✓		✗	✓		✓	✓	✓		
	P87	2	✓								+	No deficits. No evidence of functional impact.
		3	✓									
	P88	3	✓		✗	✗	✗	✗	✗	✗	–	Extensive deficits. Evidence of functional impact.
	P89	3	✓		✓	✗	✗	✓	✓	✗	+	Relatively focal deficits. Uncertain functional impact.
	P90	3	✗		✗	✓			✗	✗	–	Intellectual sequelae. Evidence of functional impact.
McKeon et al. (2016)	P91	3	✓	✓	✓	✓	✓	✗	✓	✓	–	Focal deficit. Functional impact.
	P92[b]	1		✓	✓	✗	✓	✗	✓	✓	+	Relatively focal deficits. Minimal functional impact.
		3	✓	✗	✓	✓	✓	✗	✗	✓		
	P93	2	✓	✗	✓	✓	✓	✓	✗	✓	+	Relatively focal deficits. No evidence of functional impact.
	P94	3	✓	✗	✗	✗	✓	✗	✗	✗	–	Extensive deficits.
	P95	3	✓	✗	✓	✓	✓	✗	✓	✓	–	Relatively focal deficits. Functional impact.
	P96	3	✓	✓	✓	✓	✓	✓	✓	✗	+	Focal deficit. No evidence of functional impact.

(*Continued*)

Table 2. (Continued).

Reference	ID	Time point	Cognitive domain[a]								Cognitive outcome	Outcome rationale
			IQ	Mem	Lang	Attn	WM	EF	VS	IPSp		
	P97	2	✓	✗	✓	✓	✓	✗	✓	✓	+	Relatively focal deficits. No evidence of functional impact.
Mechelhoff et al. (2015)	P98	3									+	No deficits. No evidence of functional impact.
Parratt et al. (2009)	P99	3									+	No deficits.
Pillai, Gill, Webster, Howman-Giles, and Dale (2010)	P100	NQ	✗								–	Significant intellectual sequelae .
Sakamoto et al. (2013)	P101	3			✗						+	No deficits. No evidence of functional impact.
		3			✓							
	P102	1	✗		✗				✗		–	Intellectual sequelae.
Salvucci, Devine, Hammond, and Sheth (2014)	P103	3	✓		✓						+	No deficits. No evidence of functional impact.
Sawamura et al. (2014)	P104	1							✗		+	No deficits.
		2							✗			
		2							✓			
Shimoyama, Umegaki, Agui, Kadono, and Minami (2016)	P105	1									+	No deficits. No evidence of functional impact.
Slettedal, Dahl, Sandvig, Dalmau, and Strømme (2012)	P106	3									+	No deficits. No evidence of functional impact.
Türkdoğan et al. (2014)	P107	1	✗	✗	✗	✗	✗	✗	✗	✗	–	Intellectual sequelae.
		2	✗		✓				✗			
		3	✗		✓				✗			
Tüzün et al. (2013)	P108	1		✓	✓	✓	✓	✓	✓		+	No deficits. No evidence of functional impact.
Vahter et al. (2014)	P109	2		✗	✓	✓		✗	✓	✓	+	Focal, but persistent deficit. Performance improved. Uncertain functional impact.
		3		✗	✓	✓		✓	✓	✓		
		3		✗	✓	✓		✓	✓	✓		
Domain totals		*All*										**Outcome totals**
Any time point	✗, *n* (%)	114 (76.5)	20 (24.7)	57 (55.9)	40 (35.7)	41 (41.8)	34 (38.2)	45 (48.9)	36 (33.3)	30 (46.9)		+ *n* (%): 81/109 (74.3)
	✓, *n* (%)	35 (23.5)	61 (75.3)	45 (44.1)	72 (64.3)	57 (58.2)	55 (61.8)	47 (51.1)	72 (66.7)	34 (53.1)		– *n* (%): 28/109 (25.7)
Acute	✗, *n* (%)	23 (76.7)	7 (63.6)	10 (52.6)	13 (68.4)	11 (64.7)	9 (56.3)	11 (64.7)	12 (63.2)	9 (64.3)		
	✓, *n* (%)	7 (23.3)	4 (36.4)	9 (47.4)	6 (31.6)	6 (35.3)	7 (43.8)	6 (35.3)	7 (36.8)	5 (35.7)		
Subacute	✗, *n* (%)	29 (76.3)	4 (20.0)	16 (66.7)	10 (34.5)	7 (29.2)	6 (30.0)	10 (52.6)	10 (35.7)	7 (35.0)		
	✓, *n* (%)	9 (23.7)	16 (80.0)	8 (33.3)	19 (65.5)	17 (70.8)	14 (70.0)	9 (47.4)	18 (64.3)	13 (65.0)		
Longer term	✗, *n* (%)	45 (77.6)	6 (15.0)	21 (55.3)	14 (28.6)	17 (40.5)	10 (26.3)	18 (43.9)	13 (28.3)	11 (40.7)		
	✓, *n* (%)	13 (22.4)	34 (85.0)	17 (44.7)	35 (71.4)	25 (59.5)	28 (73.7)	23 (56.1)	33 (71.7)	16 (59.3)		

Note. ✗ = domain assessed, deficit present; ✓ = domain assessed, deficit absent; + = positive/favorable outcome; – = negative/adverse outcome; 1 = acute recovery phase (within 3 months of treatment initiation); 2 = subacute recovery phase (3–12 months after treatment initiated); 3 = longer term recovery phase (any time after 12 months following treatment initiation); anti-NMDAR = anti-N-methyl-D-aspartate receptor; Attn = attention; IPSp = information processing speed; EF = executive functioning; IQ = intelligence quotient; Lang = language; Mem = memory; NQ = not quantifiable based on available information; VS = visual–spatial functions; WM = working memory.

[a]Judgment of impairments based on data where provided and interpretable. In instances where original authors' written interpretation not congruent with data provided, current authors' documented impairments based on data.

[b]Patient originally described by Hegarty and Mikli (2013); Re-assessment of same patient reported by McKeon et al. (2016).

Qualitative examination of the small patient subset assessed on multiple occasions (n = 27) suggested that neuropsychological functioning following treatment for anti-NMDAR encephalitis is often stable or clearly improves (n = 20, 74.1%). However, in a minority of patients (n = 7, 25.9%) it was apparent that patient performance across serial neuropsychological testing fluctuated, clearly deteriorated (Dogan Onugoren et al., 2016; Matricardi et al., 2016; McKeon et al., 2016), or demonstrated evidence of persistent intellectual impairment (Guo et al., 2014; Türkdoğan, Orengul, Zaimoğlu, & Ekinci, 2014). The latter cases illustrate what we would arguably consider the most severe and concerning published examples of neuropsychological sequelae associated with anti-NMDAR encephalitis.

Guo et al. (2014) report the case of a three-year-old child who was hospitalized for six months in a pediatric intensive care unit with anti-NMDAR encephalitis, and underwent 28 months of rehabilitation. She was treated within one month of symptom onset with pulse methylprednisolone therapy (30 mg kg^{-1} per dose, four doses), maintenance oral prednisolone (0.9 mg kg^{-1} perday), three months of plasmapheresis, and a combination of weekly rituximab (375 mg m^{-2}, four doses) and prolonged monthly cyclophosphamide pulse therapy (750 mg m^{-2}, 8 months), followed by three months of azathioprine. Evidence of intellectual impairment was initially quantified during her rehabilitation (full-scale intelligence quotient, FSIQ, 62, <1st percentile), with similar findings reported three years after symptom onset. Authors also reported prolonged, intractable oral dyskinesia and generalized dystonia in this patient.

The 15-year-old patient described by Türkdoğan et al. (2014) demonstrated evidence of impaired intellectual functioning at three assessments conducted two, seven, and 24 months after treatment was initiated. By this last point of follow-up, the impairments were mild but ongoing (FSIQ 78, 7th percentile). Treatment was delayed in this patient by approximately three months. She was subsequently treated with intravenous immunoglobulin (IVIg;1 g kg^{-1} per day, three days) and pulse methylprednisolone (1 g per day) followed by five days of pulse therapy, and oral prednisolone (1 mg kg^{-1} per day, tapered over three years). No second-line immunotherapies were reported. Authors attributed their patient's limited cognitive recovery to the late onset of immunotherapy and presence of progressive cerebral atrophy.

Predictors of neuropsychological outcomes

Adverse and more favorable overall cognitive outcomes as classified by the current study were recorded in 25.7 and 74.3% of our sample, respectively (Table 2). Table 4 presents the results of chi square analyses investigating the significance of relationships between neuropsychological outcomes and various putative predictive factors. These analyses revealed patients having almost eight times the odds of an adverse neuropsychological outcome where treatment was initiated more than three months after onset of encephalitis, compared to those who received treatment earlier (61.5% vs. 17%; odds ratio, OR, 7.82, and 95% confidence interval, CI, [2.07–29.5]).

Discussion

Analyzing data from 44 studies of 109 patients from 16 countries, this systematic review sought to investigate the neuropsychological functioning of individuals treated for anti-NMDAR encephalitis. We aimed to describe the nature and frequency of cognitive deficits experienced by patients across various points of recovery. We also explored the association between demographic and clinical factors and neuropsychological outcomes following treatment. This is the first and most comprehensive literature summary describing cognitive outcomes in this complex population.

Summary of results

The majority of patients treated for anti-NMDAR encephalitis experience significant cognitive sequelae during recovery. More specifically, we identified diverse neuropsychological deficits in 76.5% (n = 114/149) of assessments conducted with anti-NMDAR encephalitis patients at any point following treatment. High rates of patients from our sample presented with posttreatment neuropsychological impairments at acute (76.7%; n = 23/30), subacute (76.3%; n = 29/38), and longer term (77.6%; n = 45/58) time-points. Although difficult to account for the impact of publication bias, these rates of cognitive impairment are substantial. Results lend further support to the notion derived from smaller case series (Finke et al., 2012; McKeon et al., 2016) that neuropsychological sequelae of variable severity can persist despite adequate treatment and lengthy recovery periods, and that early treatment is the most important clinical factor to a favorable cognitive outcome.

Affected cognitive domains

Our analyses revealed that patients recovering from anti-NMDAR encephalitis experience dysfunction in a variety of cognitive domains. The neuropsychological

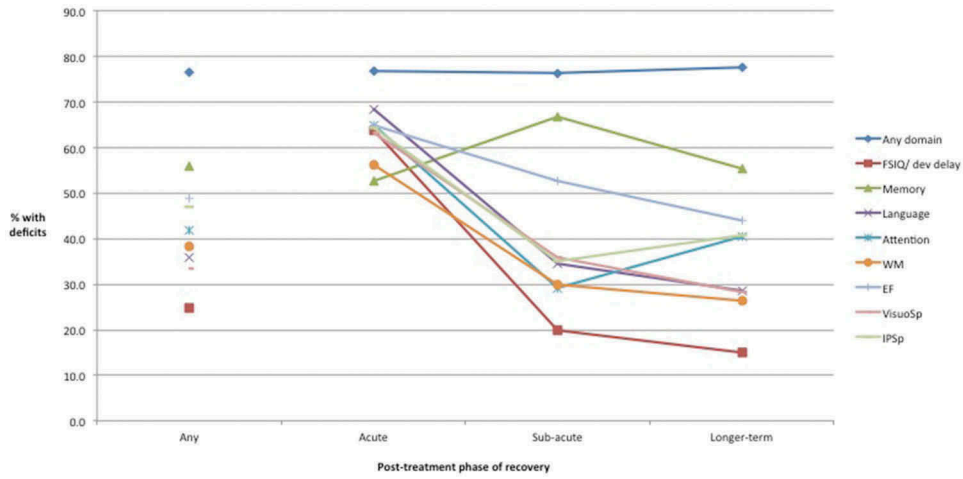

Figure 4. Frequency of specific cognitive deficits identified at various points of recovery from anti-NMDA receptor encephalitis. Anti-NMDA = anti-N-methyl-D-aspartate; FSIQ = full-scale intelligence quotient; WM = working memory; EF = executive functioning; VisuoSp = visuospatial; IPSp = information processing speed. To view a color version of this figure, please see the online issue of the Journal.

profile of patients recovering from anti-NMDAR encephalitis was diverse, ranging from an absence of deficits to global and debilitating cognitive dysfunction. In line with the distribution and functions of NMDARs, core deficits of anti-NMDAR encephalitis appear to encompass the cognitive domains of episodic memory and executive functioning. These abilities were the most commonly affected domains on assessments administered at any point during recovery. More specifically, of patients assessed at any time following treatment initiation on measures of verbal and visual episodic memory and various aspects of executive functioning, 55.9 (n = 57/102) and 48.9% (n = 45/92) demonstrated impaired performance in these areas, respectively.

There were also substantial proportions of patients identified at all points of recovery with deficits of working memory (38.2%; n = 34/89), language (35.7%; n = 40/112), various aspects of visual–spatial (33.3%; n = 36/108) and attentional (41.8%; n = 41/98) functions, processing speed (46.9%; n = 30/64), and overall intellectual functioning (24.7%; n = 20/81). The balance of evidence suggested preservation of overall intellect. However, persistent global cognitive deficits were identified in two patients with unremarkable premorbid medical and psychiatric histories (Guo et al., 2014; Türkdoğan et al., 2014).

High rates of persistent impairments in executive functioning and episodic memory following NMDAR system pathology are congruent with the central roles of this system in fast, excitatory synaptic communication, and the facilitation of LTP and LTD (Kalia et al., 2008; Molnar, 2008; Paoletti & Neyton, 2007). These cognitive deficits are also consistent with ubiquitous NMDAR expression, particularly high density within the mammalian hippocampus and frontal cortex (Monaghan & Cotman, 1985), and known effects of NMDAR antagonist administration (Hetem, Danion, Diemunsch, & Brandt, 2000; Krystal et al., 2000; Malhotra et al., 1996; Morgan, Mofeez, Brandner, Bromley, & Curran, 2004).

This review also identified emerging evidence of dysfunctional social cognition in patients recovering from anti-NMDAR encephalitis (Bach, 2014; McKeon et al., 2016). In studies of patients with schizophrenia there is robust evidence that impairment in these skills contributes more to the prediction of poor social and vocational outcomes than performance on standard neuropsychological measures alone (Couture, Penn, & Roberts, 2006; Green & Horan, 2010; Martin, Robinson, Dzafic, Reutens, & Mowry, 2014; Nestor, Niznikiewicz, & McCarley, 2010; Pijnenborg et al., 2009). Impaired social cognition may also undermine functional recovery in anti-NMDAR encephalitis, although this represents an under-researched area within this population.

Cognitive dysfunction at different phases of recovery

Despite the high rates of neuropsychological dysfunction identified in this population, our study indicated that the majority of patients (74.3%) could be classified as achieving a relatively favorable outcome from a cognitive perspective. Our outcomes classification criteria considered the presence and pervasiveness of

Table 3. Results of chi square analyses examining the frequency of specific cognitive deficits identified at various points of recovery from anti-NMDA receptor encephalitis.

		Deficit absent		Deficit present						
Cognitive domain		*n*	%	*n*	%	Comparison	χ^2	*p*	OR	95% CI
Any domain	1	7	23.3	23	76.7	1 vs. 2	0.001	.973	—	—
	2	9	23.7	29	76.3	2 vs. 3	0.021	.885	—	—
	3	13	22.4	45	77.6	1 vs. 3	0.010	.922	—	—
IQ	1	4	36.4	7	63.6	1 vs. 2	5.90	.023	.143	[.028, .741]
	2	16	80.0	4	20.0	2 vs. 3	0.240	.718	—	—
	3	34	85.0	6	15.0	1 vs. 3	9.66	.002	.101	[.022, .454]
Memory	1	9	47.4	10	52.6	1 vs. 2	0.874	.350	—	—
	2	8	33.3	16	66.7	2 vs. 3	0.795	.373	—	—
	3	17	44.7	21	55.3	1 vs. 3	0.035	.851	—	—
Language	1	6	31.6	13	68.4	1 vs. 2	5.29	.021	.243	[.071, .834]
	2	19	65.5	10	34.5	2 vs. 3	0.299	.585	—	—
	3	35	71.4	14	28.6	1 vs. 3	9.08	.003	.185	[.059, .582]
Attention	1	6	35.3	11	64.7	1 vs. 2	5.10	.024	.225	[.060, .848]
	2	17	70.8	7	29.2	2 vs. 3	0.844	.358	—	—
	3	25	59.5	17	40.5	1 vs. 3	2.84	.091	—	—
Working memory	1	7	43.8	9	56.3	1 vs. 2	2.52	.112	—	—
	2	14	70.0	6	30.0	2 vs. 3	0.089	.765	—	—
	3	28	73.7	10	26.3	1 vs. 3	4.42	.035	.278	[.082, .944]
Executive functioning	1	6	35.3	11	64.7	1 vs. 2	0.538	.463	—	—
	2	9	47.4	10	52.6	2 vs. 3	0.397	.528	—	—
	3	23	56.1	18	43.9	1 vs. 3	2.08	.149	—	—
Visuospatial functions	1	7	36.8	12	63.2	1 vs. 2	3.42	.064	—	—
	2	18	64.3	10	35.7	2 vs. 3	0.451	.502	—	—
	3	33	71.7	13	28.3	1 vs. 3	6.91	.009	.230	[.074, .713]
Processing speed	1	5	35.7	9	64.3	1 vs. 2	2.83	.092	—	—
	2	13	65.0	7	35.0	2 vs. 3	0.160	.689	—	—
	3	16	59.3	11	40.7	1 vs. 3	2.04	.153	—	—

Note. NMDA = N-methyl-D-aspartate; OR = odds ratio; CI = confidence interval. 1 = acute recovery phase (within 3 months of treatment initiation); 2 = subacute recovery phase (between 3 and 12 months after treatment initiated); 3 = longer term recovery phase (any time after 12 months following treatment initiation).

cognitive deficits, and impact upon functioning. However, the cross sectional nature of the current study did not allow for the impact of relapses upon cognition to be reliably investigated. Symptom relapses may have cumulative consequences for cognition. Patients who experienced relapses were reported by three studies (Martin-Monzon, Trujillo-Pozo, & Romero, 2012; Matricardi et al., 2016; McKeon et al., 2016), and only one of these described the results of a patient assessed on multiple occasions. Interestingly, this patient reportedly achieved full recovery of cognitive deficits despite multiple relapses and evidence of bilateral temporal lobe atrophy (Martin-Monzon et al., 2012). Clearly the anti-NMDAR encephalitis literature would benefit from further longitudinal neuropsychological studies including patients with relapsing remitting forms of the illness.

Consideration of all studies reporting the results of serial neuropsychological assessments suggested that the course of cognitive dysfunction is often mild as quantitatively measured, but that a minority of patients will demonstrate evidence of severe, persistent, and pervasive deficits. Additional prospective neuropsychological studies of larger patient cohorts are required to provide further clarity with respect to factors predictive of cognitive trajectories.

Our systematic review of available cases lends very strong support to the importance of prompt diagnosis and initiation of appropriate intervention in reducing the likelihood of severe neuropsychological sequelae. Results suggested that the following variables were less relevant to cognitive outcomes in this population: age, gender, abnormal MRI/EEG findings, disease etiology, use of more aggressive immunotherapies, life-threatening symptoms, and seizure activity. The significance of MRI and EEG results arguably requires further more sophisticated and detailed study, as has been initiated recently (Heine et al., 2015). Specifically, it has been shown that some patients recovering from anti-NMDAR encephalitis show significantly reduced functional connectivity between the hippocampus and the anterior default mode network, which correlates with memory deficits (Finke et al., 2013). Additionally, some patients with anti-NMDAR encephalitis exhibit significant atrophy and microstructural damage of the hippocampus, with both measures likewise predicting the degree of memory deficits (Finke et al., 2016).

Methodological considerations

This review provides the most up-to-date and comprehensive synthesis of literature pertaining to cognitive

Table 4. Results of chi square analyses examining the relationship between cognitive outcome and various putative predictive factors.

	Favorable outcome		Poor outcome					
Clinical variables	*n*	%	*n*	%	χ^2	*p*	OR	95% CI
Gender								
Male	12	66.7	6	33.3	0.660	.417	—	—
Female	69	75.8	22	24.2				
Age								
Child or adolescent	27	71.1	11	28.9	0.325	.569	—	—
Adult	54	76.1	17	23.9				
MRI abnormality								
Absent	45	73.8	16	26.2	0.014	.905	—	—
Present	32	72.7	12	27.3				
EEG abnormality								
Absent	3	75.0	1	25.0	0.039	1.000	—	—
Present	38	70.4	16	29.6				
Seizures								
Absent	19	70.4	8	29.6	0.292	.589	—	—
Present	62	75.6	20	24.4				
ICU treatment/severe AI								
Absent	24	64.9	13	35.1	2.309	.129	—	—
Present	26	81.3	6	18.8				
Treatment timing								
Early	44	83.0	9	17.0	10.84	.003	7.82	[2.07, 29.5]
Late	5	38.5	8	61.5				
Nature of treatment								
Solely 1st line treatment	62	76.5	19	23.5	0.822	.364	—	—
2nd line treatment	19	67.9	9	32.1				
Etiology								
Idiopathic	62	72.1	24	27.9	0.863	.353	—	—
Paraneoplastic	18	81.8	4	18.2				

Note. OR = odds ratio; CI = confidence interval; AI = autonomic instability; ICU = intensive care unit; MRI = magnetic resonance imaging; EEG = electroencephalography.

functioning following treatment for anti-NMDAR encephalitis. The study conformed to PRISMA guidelines (Moher et al., 2009) and was conducted with measures in place directed towards preventing review-level bias. Specifically, search methodology was designed to be as inclusive as possible with regard to terms and databases utilized. Furthermore, there were no language restrictions, and measures were implemented to ensure that only studies of neuropsychological functioning were included.

Results must, however, be interpreted in the context of several limitations of the present study and the anti-NMDAR encephalitis literature. Firstly, due to inconsistent reporting standards it is possible that patients without conservatively defined neuropsychological impairments may have been erroneously included in our estimation of the frequency of cognitive dysfunction after anti-NMDAR encephalitis. Minimal impact upon interpretation is anticipated given that studies were required to demonstrate evidence of formal testing. This was implemented to increase the likelihood that where deficits were reported, a qualified clinician was responsible for interpretation. We anticipated that this would assist in reducing the impact of publication bias by including studies of patients where "no deficits" were apparent. Nonetheless, future researchers are encouraged to be more specific regarding the measures administered and the definition of terms such as "impairment," "deficit," or "weakness."

Secondly, our cross-sectional review methodology did not permit advancement in our understanding of the impact of relapses upon cognition. Similarly, whilst we suggest that deficits of episodic memory, processing speed, and executive functioning might be less amenable to treatment, our study design precluded definitive conclusions regarding the longitudinal course of cognitive dysfunction. Future neuropsychological studies with this population must specify when assessments were administered in relation to treatment initiation and how cognitive functioning progressed over time.

Thirdly, this analysis did not account for several patient characteristics. Treatments administered in addition to immunotherapy such as antipsychotics or anticonvulsants were not controlled for. It is difficult to establish the direction of potential bias, as newer and older medications from both drug classes are differentially associated with positive and adverse cognitive side effects (Eddy, Rickards, & Cavanna, 2011; Hill, Bishop, Palumbo, & Sweeney, 2010; Hori et al., 2006; Park & Kwon, 2008). There was a preponderance of females (83.5%) and adults (65.1%) in the current sample. Although consistent with known demographics of the syndrome (Dalmau et al., 2011; Titulaer et al.,

2013), results may be less applicable to males, children, and adolescents.

Finally, "pure" measures of specific cognitive functions are rare, and the majority of neuropsychological tests assess multiple abilities (Lezak et al., 2012). As such, authors of included studies occasionally varied in interpretation of skills measured by instruments. Therefore, where studies did not explicitly name measures, additional but unreported domains may have been affected or spared in some patients. Similarly, for pragmatic purposes, this review focused on the major cognitive domains affected following anti-NMDAR encephalitis. It seems likely that the relative contributions of various subprocesses comprising these functions will be complex, particularly in relation to multifactorial domains such as attention and executive functioning. This was not, however, addressed by the current study. Moreover, there was only limited scope to consider factors such as premorbid cognitive functioning, motivational/behavioral information, collateral information, and general coherence of the clinical picture.

Implications for clinical practice and research

In supporting claims that cognitive deficits are prevalent amongst patients recovering from anti-NMDAR encephalitis, this study has implications for understanding and planning the longer term rehabilitation needs of this population. Comprehensive neuropsychological assessments are important for these patients. Given potentially global dysfunction, neuropsychologists are encouraged to think broadly with regard to test selection. Our results indicate that this will be particularly relevant during the acute illness recovery phase. As a minimum requirement, assessments of verbal and visual episodic memory, information processing speed, and multiple aspects of executive functioning should be administered, as performance in these domains is commonly impaired during recovery. Moreover, impairments in these skills may be among the most tenacious neuropsychological deficits following anti-NMDAR encephalitis.

Serial neuropsychological assessments are likely to be clinically relevant with respect to updating rehabilitation plans and monitoring for relapse. From a research perspective, this review identified reporting of longitudinal cognitive data as a significant literature shortcoming that impeded detailed prognostic analysis of neuropsychological dysfunction. For patients and their families, such data seem significant for promoting understanding and future expectations. Additional studies reporting longitudinal neuropsychological data would represent valuable contributions to the anti-NMDAR encephalitis knowledge base. At present, little is known regarding predictors of neuropsychological trajectories beyond the analyses of Finke et al. (2012) and the current cross-sectional study, where early treatment has been associated with significantly better cognitive outcomes.

Given the potentially devastating functional impact of neuropsychological dysfunction on the daily lives of those affected by anti-NMDAR encephalitis, additional studies describing detailed outcomes of cognitive rehabilitation interventions in this population are needed. To the knowledge of the authors, only four published studies of variable detail reference cognitive rehabilitation for these patients (Bach, 2014; Bradley, 2015; Guo et al., 2014; Tham & Kong, 2012). Given identified heterogeneity amongst patients with respect to cognitive functioning, it is likely that individually tailored interventions (e.g., Bach, 2014; Bradley, 2015) will be of greatest utility in this group. Evidence for the effectiveness of specific strategies or responsiveness of cognitive domains to rehabilitation is, however, lacking at present.

Summary and conclusions

Neuropsychological dysfunction is experienced by most patients recovering from anti-NMDAR encephalitis, and early treatment appears to be important to optimize cognitive recovery. Consistent with the diverse roles and widespread distribution of the NMDA receptors, neuropsychological profiles were variable. The most commonly observed deficits across all points of recovery were in the domains of episodic memory and executive functioning, followed by attention and processing speed. Episodic memory, executive functioning, and processing speed deficits appear to be particularly persistent. The reliability of our conclusions are, however, limited by significant shortcomings of the literature. Additional studies reporting clear and consistently defined neuropsychological data are required, and there is a clear need for further longitudinal research in this field. The impact of disease relapse upon cognitive functioning is poorly understood at present. Future studies of neuropsychological outcomes and social cognition in patients recovering from anti-NMDAR encephalitis are needed to inform rehabilitation and minimize disability arising from this autoimmune disorder.

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