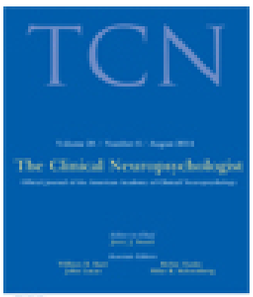

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Neuropsychological characterization of three adolescent females with anti-NMDA receptor encephalitis in the acute, post-acute, and chronic phases: an inter-institutional case series

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ABSTRACT

Objective: Anti-*N*-methyl-D-aspartate (anti-NMDA) receptor encephalitis is an acute, immune-mediated paraneoplastic syndrome that often presents with psychobehavioral changes, abnormal movements, autonomic instability, seizures, and cognitive dysfunction. While the disease continues to be more readily identified and appropriately treated, the course of cognitive deficits from the acute to post-acute to chronic phase has not been well described, particularly in the pediatric population. This case series describes the neuropsychological functioning of three adolescent females with anti-NMDA receptor encephalitis from its early presentation to long-term follow-up.

Method: All three cases are adolescent females with antibody-confirmed anti-NMDA receptor encephalitis. A review of the literature is provided summarizing the disorder and its known cognitive sequelae, pathophysiology, treatment, and prognostic factors, as well as each patient's relevant history, symptom presentation, and disease course. Neuropsychological functioning of each patient was evaluated from her initial inpatient hospitalization to long-term follow-up (3.5–12 months after acute evaluation).

Results: All three patients demonstrated clear improvement in cognitive functioning during the course of their recovery, though selected deficits in executive functioning, fine motor dexterity, language, and memory were observed at long-term follow-up in some of our patients.

Conclusions: Findings are consistent with studies in adults that found cognitive deficits following anti-NMDA receptor encephalitis. Though gradual recovery was noted over time, all three patients reported no clinically significant difficulties during their final evaluation, despite showing mild impairment in some areas, emphasizing the importance of ongoing neuropsychological follow-up.

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Introduction

Anti-*N*-methyl-D-aspartate (anti-NMDA) receptor encephalitis is an acute, immune-mediated paraneoplastic syndrome first characterized by Dalmau and colleagues in 2005 (Dalmau et al., 2007; Guo et al., 2014). While some literature now exists on the neuropsychological impact of the condition, little has been published on how neuropsychological functioning evolves from the acute to post-acute to chronic phase of this disease in a cohort of adolescents. This case series characterizes the neuropsychological functioning of three adolescent females with antibody-confirmed anti-NMDA receptor encephalitis.

Anti-NMDA receptor encephalitis often initially presents as nonspecific flu-like symptoms (e.g. fever, fatigue, and/or headache), lasting a mean of 5 days (Bach, 2014). Though the disease course can vary considerably, most individuals experience a combination of acute psychobehavioral changes (e.g. anxiety, depression, agitation, avoidance, withdrawal, fear, mood lability, and apathy), cognitive dysfunction (e.g. memory loss and/or difficulty using everyday objects), and unusual thoughts and behaviors (e.g. delirium, disorganized thinking, obsessive compulsive behaviors, hypersexuality, delusional or paranoid thoughts, and/or auditory and visual hallucinations) within 2 weeks of the flu-like prodrome (Bach, 2014; Dalmau et al., 2008; Guo et al., 2014; Irani et al., 2010; Keller, Roitman, Ben-Hur, Bonne, & Lotan, 2014; Titulaer et al., 2013; Vahter et al., 2014). Cataplexy-like symptoms (e.g. mutism, akinesia, unresponsiveness, bizarre and inappropriate smiling, and/or dystonic posturing) may also follow (Bach, 2014). During its later stages, movement disorders (e.g. orofacial dyskinesias, sustained jaw movements, teeth clenching, jaw-opening dystonia, grimacing, intermittent ocular deviation or disconjugation, athetoid dystonic movements, and/or dancing-like movements of the arms), alterations of consciousness, speech problems, and autonomic instability may be present (Bach, 2014; Dalmau et al., 2008; Guo et al., 2014; Irani et al., 2010; Keller et al., 2014; Titulaer et al., 2013; Vahter et al., 2014). Seizures are also present in 78% of patients, but are rarely the first presenting symptom (Dalmau et al., 2008). While adult patients most often present with prominent psychiatric symptoms, children diagnosed with the disease typically present with more neurological and movement symptoms (e.g. ataxia and/or hemiparesis) and sometimes seizures (Dalmau, Lancaster, Martinez-Hernandez, Rosenfeld, & Balice-Gordon, 2011; Titulaer et al., 2013). Though anti-NMDA receptor encephalitis presents in both children and adults, it has become a leading cause of autoimmune encephalitis in the pediatric population, with 40% of patients being younger than 18 years of age (Armangue, Petit-Pedrol, & Dalmau, 2012).

Of the few studies that have examined neuropsychological functioning in anti-NMDA receptor encephalitis, most have focused on adult populations and conducted testing at only a single time point. Finke et al. described persistent impairments in attention, episodic memory, and/or executive functioning, in eight of the nine adult patients in the chronic phase of recovery (median 43 months after disease onset) (Finke, Kopp, Prüss, et al., 2012). In a sample of two adults who underwent formal testing, Bach found persistent memory and executive functioning deficits, though the severity of impairment varied considerably between the two patients (Bach, 2014). Acute deficits in both verbal and visual memory were reported in an adult patient, which resolved a month later following treatment (Marcos-Arribas, Almonacid, & Dolado, 2013). Acute impairment in verbal memory and executive functioning was observed in another adult patient, with persistent impairment in verbal memory at long-term follow-up (608 days after disease onset) (Vahter et al., 2014). Deficits

in attention, executive functioning, verbal fluency, and rapid naming were seen in two pediatric patients (one patient at 10 months after disease onset and the other at 21 months post-onset); the first patient showed significant improvement 22 months after onset, with many performances returning to the patient's estimated premorbid baseline (Iadisernia et al., 2012). Persistent deficits in working memory and/or attention have been similarly reported in other studies (Azizyan, Albrektson, Maya, Pressman, & Moser, 2014; Dalmau et al., 2008; Poloni et al., 2010). In sum, most studies have documented persistent memory and executive deficits for adults in the chronic phase of anti-NMDA receptor encephalitis. To our knowledge, little has been published regarding adolescents with this condition, and furthermore, more research is needed to further characterize how cognitive dysfunction in anti-NMDA receptor encephalitis unfolds over time.

Anti-NMDA receptor encephalitis is an autoimmune reaction primarily against the NR1 subunit of NMDA receptors, which plays a critical role in synaptic transmission and learning-related plasticity and is highly concentrated in the forebrain, limbic system, and hypothalamus (Bach, 2014; Chapman & Vause, 2011; Li & Tzien, 2009; Onur et al., 2012). The onset of symptoms of anti-NMDA receptor encephalitis is associated with a unique antibody binding to the extracellular portion of the NMDA receptor, resulting in the capping and internalization of receptors from the synaptic surface (Dalmau et al., 2007; Hughes et al., 2010). This leads to a decrease in receptor density and diminished glutamatergic function (Azizyan et al., 2014; Dalmau et al., 2007; Hughes et al., 2010). Persistent memory deficits in the acute phase of anti-NMDA receptor encephalitis are consistent with the disruption of synaptic processes in limbic structures, particularly the hippocampus, which are essential to aspects of learning and memory (Bach, 2014).

Though results of routine clinical MRI are often unremarkable in this population, multimodal MRI, including T1- and T2-weighted structural imaging, analysis of resting-state functional connectivity, analysis of white matter using diffusion tensor imaging, and analysis of gray matter using voxel-based morphometry has been associated with significantly reduced functional connectivity of the left and right hippocampi with the anterior default mode network and extensive white matter changes, most prominent in the cingulum (Finke, Kopp, Pruss, et al., 2012). Anti-NMDA receptor encephalitis has also been associated with hippocampal volume reduction and bilateral hippocampal microstructural integrity impairment, though the frequency of MRI abnormalities is less common in children than adults (Armangue et al., 2012; Finke et al., 2016).

Literature examining the long-term prognostic factors in anti-NMDA receptor encephalitis is somewhat limited but growing. While most studies demonstrate a favorable outcome, others report persistent deficits in patients. In a multi-institutional observational study of 577 patients, 81% demonstrated substantial neurological improvement in the first 24 months following the diagnosis, and 12% of all patients experienced a relapse requiring continued immunotherapy (Titulaer et al., 2013). Other studies report a relapse rate as high as 25% (Dalmau et al., 2008; Titulaer et al., 2013). Chapman and Vause caution, however, that more than 85% of patients who eventually make substantial neurological improvement continue to show mild persistent deficits, including psychiatric symptoms, memory loss, and impairments in attention and executive functioning (Chapman & Vause, 2011). Factors associated with better outcome and reduced likelihood of relapse include the presence of a detectable tumor (most commonly ovarian teratoma), early treatment (i.e. early immunotherapy and/or prompt tumor removal), and severity that does not require intensive care (Bach, 2014;

Dalmau et al., 2008; Titulaer et al., 2013). Clinical improvement is also associated with a decrease in cerebrospinal fluid (CSF) and serum antibody titers, though the sensitivity of NMDA receptor antibody testing is higher in CSF than in serum (Dalmau et al., 2008; Gresa-Arribas et al., 2014). Anti-NMDA receptor encephalitis is fatal in roughly 5% of cases, typically the result of neurological and autonomic dysfunction (Keller et al., 2014).

Anti-NMDA receptor encephalitis continues to be more readily identified and appropriately treated, but its impact on neuropsychological functioning requires more investigation. The course of cognitive deficits from the acute to post-acute to chronic phase of the disease has not been well described, particularly in the pediatric population. This case series describes the neuropsychological functioning of three adolescent females with anti-NMDA receptor encephalitis from its early presentation to long-term follow-up.

Methods

Three adolescent females with antibody-confirmed anti-NMDA receptor encephalitis were selected from two different institutions in the Midwestern United States. For all three patients, the presence of NMDAR antibodies was confirmed by a CSF titer, though the laboratory did not provide exact values. Clinical details of the patients are described in the case reports below. Flexible neuropsychological test batteries were used that assessed some combination of intelligence, motor/sensory skills, visual-spatial skills, attention, executive functioning, language, memory, academic functioning, and emotional functioning at various points during the patients' recovery course (for details, see Tables 1–3).

Neuropsychological evaluations were conducted for all patients in the acute phase (within approximately 4–6 weeks of symptom onset). Two of the three patients underwent a second, post-acute neuropsychological evaluation following administration of first-line treatment (2–6 months after symptom onset). All patients underwent a neuropsychological evaluation in the chronic phase after most or all treatments were discontinued and the patients had returned to their premorbid activities (approximately 6–24 months after symptom onset).

The test results were categorized as broadly average (within 1 SD of the mean), borderline (1–2 SD below the mean), impaired (2–3 SD below the mean), or severely impaired (more than 3 SD below the mean). When used to describe our patients' performance, 'clinically significant' refers to scores at or below the borderline range, and 'significant improvement' refers to an increase of at least 2/3 SD in scores.

Case reports

Case 1 (DF)

Background

DF was a high-functioning and independent 17-year-old, right-handed young woman with no reported previous psychiatric history or history of learning or attention problems. She was an average to above average high school student (3.3 GPA and 28 ACT score) from a family of middle to upper middle socioeconomic status (SES). In addition to attending high school full time, DF also took nursing courses at a local college and held a part-time job when she began experiencing periods of dizziness and disorientation approximately 2 weeks prior to her first ED admission. Her family also retrospectively reported observing changes

in DF's behavior, characterized by increased irritability and abruptness in her interactions with teachers, as well as perseverative behaviors (i.e. repeatedly questioning her boyfriend). She initially presented to the ED after periods of dizziness and disorientation persisted and she began to have slurred speech. During her admission, head CT, brain MRI, neck MRA, and EKG were conducted and read as normal. A tilt table test was abnormal, and DF was diagnosed with postural orthostatic tachycardia syndrome and was discharged. Over the next 2 weeks, DF continued to experience a number of symptoms, including dizziness, tachycardia, slurred speech, and delirium (e.g. not recognizing her parents or knowing where she was). She also reported feeling like everything was moving very fast then very slowly and having intermittent, unprovoked giddiness. Clusters of these symptoms occurred 1–2 times per day before becoming almost continuous. DF was readmitted to the hospital. During her second hospitalization, DF demonstrated marked variability in her behavior, ranging from slowed interactions and lethargy to clear distress and agitation. There were also ongoing episodes of confusion, perseverative speech, and giddiness, as well as some visual hallucinations. Long-term electroencephalogram (EEG) monitoring showed right frontal and bi-occipital slowing, and she was started on anti-epileptic drug (AED) therapy. Prior to her discharge, an inpatient neuropsychological evaluation was conducted, and blood and CSF panels were conducted.

Acute evaluation

Behavior observations. During her acute evaluation, DF demonstrated perseverative speech and fluctuating cognitive status, with marked confusion at one point. She also exhibited considerable impulsivity and distractibility.

Neuropsychological functioning. Results of cognitive testing suggested average estimated premorbid cognitive functioning with comparable verbal and visual-spatial skills (see Table 1). Observationally, DF's attention fluctuated considerably throughout testing, and she was easily distracted by external stimuli and her own thoughts. DF was also impulsive and perseverative across tasks. Although basic visual-spatial sequencing was intact, DF demonstrated impaired cognitive flexibility. She was perseverative on both verbal and visual fluency tasks. DF's visual-spatial perception was intact, but her visual-motor construction was impaired due to her impulsive response style. DF's performance on a list-learning task was in the borderline range with limited learning over trials. Retrieval-based memory was impaired and she did not benefit from cueing, which is consistent with DF's fluctuating attention observed during testing.

Post-acute evaluation

Interim history. On the evening of DF's discharge from her second hospitalization, she experienced a prolonged seizure, lasting approximately 10 min. The following day, she experienced a briefer (i.e. approximately 1–2 min) seizure. She was started on a new AED. DF continued to have behavioral outbursts and was readmitted to the hospital after experiencing a third (8–10 min) seizure 3 days after her discharge. Upon admission, DF's CSF panel was confirmed positive for NMDAR antibodies, and immunotherapy with IV steroids and IVIG was initiated (4–5 weeks after symptom onset). A serum titer was also positive for NMDAR antibodies (1:20, reference range <1:10), and DF's CSF panel showed abnormally elevated lymphocytes (98, reference range 40–80). CSF levels of protein (28, reference range 15–45 mg/dL), glucose

Table 1. Summary of neuropsychological measures for case 1 (DF) at all evaluations.

Cognitive domain	Measure		Acute	Post-acute	Chronic
Intelligence:	WAIS-IV				
		SIM		(7)	
		VOC		(8)	
		INFO	(9)	(11)	
		BD		(5)	(13)
		MR	(11)	(11)	
		VP		(7)	
		DS		(6)	
		ARITH		(8)	
		SS		(12)	
		CD		(12)	
Motor/sensory:	Grooved Pegboard				
		DOM	108	119	
		NDOM	97	108	
Visual-spatial:	DTVP		89		
	DTVMI		<45	86	86
Attention:	CPT-II				
		Omissions		T-46	
		Commissions		T-46	
Executive functioning:	Trail Making Test				
		Part A	101	107	114
		Part B	62	120	129
	TOL-DX				
		Total Move		≤60	66
		Total Correct		72	86
	DKEFS Design Fluency				
		FDTC	(12)		
		EDOTC	(5)		
		STC	(8)		
Language:	MAE				
		COWA	58		139
		Token Test		<1%	2%
	BNT			67	74
Memory:	CVLT-II				
		Learning	80	80	103
		SD Recall	70	78	85
		LD Recall	63	70	93
		LD Recog.	d/c	63	70
	WMS-IV Logical Memory				
		LM I		(11)	
		LM II		(7)	
		LMR		>75%	
	WMS-IV Visual Reproduction				
		VR I		(10)	
		VR II		(8)	
		VRR		17–25%	
Academic functioning:	WJ-III				
		LW		93	
		CA		108	
		SP		99	
Emotional functioning:	CDI-2			Min. Sxs	
	RCMAS-2			Min. Sxs	

Abbreviations: WAIS-IV: Wechsler Adult Intelligence Scales-IV; SIM: Similarities; VOC: Vocabulary; INFO: Information; BD: Block Design; MR: Matrix Reasoning; VP: Visual Puzzles; DS: Digit Span; ARITH: Arithmetic; SS: Symbol Search; CD: Coding; DOM: Dominant hand; NDOM: Nondominant hand; DTVP: Beery-Buktenica Developmental Test of Visual Perception; DTVMI: Beery-Buktenica Developmental Test of Visual-Motor Integration; JLO: Benton Judgment of Line Orientation; CPT-II: Conners Continuous Performance Test-II; TOL-DX: Tower of LondonDX-2; RCFT: Rey-Osterrieth Complex Figure Test; DKEFS: Delis-Kaplan Executive Functioning System; VS: Visual Scanning; NS: Number Sequencing; LS: Letter Sequencing; NLS: Number-Letter Sequencing; MS: Motor Speed; FDTC: Filled Dots Total Correct; EDOTC: Empty Dots Only Total Correct; STC: Switching Total Correct; CWI: Color-Word Interference; CN: Color Naming; WR: Word Reading; TAS: Total Achievement Score; LFTC: Letter Fluency Total Correct; CFTC: Category Fluency Total Correct; CSTC: Category Switching Total Correct; CSTA: Category Switching Total Accuracy; SDMT: Symbol Digit Modalities Test; MAE: Multilingual Aphasia Examination; COWA: Controlled Oral Word Association; SR: Sentence Repetition; BNT: Boston Naming Test; ICSOR: Iowa-Chapman Speed of Reading; PPVT-4:

Peabody Picture Vocabulary Test-4; CVLT-II: California Verbal Learning Test-II; HVLT-R: Hopkins Verbal Learning Test-Revised; RAVLT: Rey Auditory Verbal Learning Test; SD: Short-Delay; LD: Long Delay; Recog.: Recognition; WMS-III/IV: Wechsler Memory Scales-III/IV; LM-I/II: Logical Memory-I/II; LMR: Logical Memory Recognition; VR-I/II: Visual Reproduction-I/II; VRR: Visual Reproduction Recognition; FWD: Forward; BKWD: Backward; BVRT: Benton Visual Retention Test; WRAT-4: Wide-Range Achievement Test-4; WR: Word Reading; MC: Math Computation; SP: Spelling; WJ-III: Woodcock-Johnson Tests of Achievement-III; LW: Letter-Word Identification; CA: Calculation; BDI-FS: Beck Depression Inventory Fast Screen; BDI-II: Beck Depression Inventory-II; BAI: Beck Anxiety Inventory; CDI-2: Children's Depression Inventory-2; RCMAS-2: Revised Children's Manifest Anxiety Scale-2; Nml: Normal; d/c: discontinued; Sev: Severely; Imp: Impaired; Bdl: Borderline; Min: Minimal; and Sxs: Symptoms.
Scores: These scores indicate performance compared to other same-aged individuals. Standard scores have an average range of 85–115. Scaled scores (in parentheses) have an average range of 7–13. *T*-scores (*T*-#) have an average range of 40–60. Percentile ranks show how well an individual performed compared to a group of individuals of the same age. Scores are shaded to indicate level of impairment according to the following scale:

Average or better/normal performance
Low average performance
Borderline performance
Impaired performance
Severely impaired performance or discontinued task

(53, reference range 40–80 mg/dL), and total nucleated cells (4, reference range 0–5/uL) were shown to be within normal limits. No information regarding oligoclonal bands or multiple sclerosis screening was available in DF's laboratory records. A pelvic ultrasound was read as normal. During her admission, DF demonstrated ongoing emotional lability, aggression, confusion, perseverative speech, posturing and repetitive hand movements, and echolalia. Long-term EEG monitoring showed continued right frontal slowing, though this was improved from her previous study. Repeat brain MRI was read as normal. By the sixth day of her admission, DF's symptoms were improving on steroid treatment. After a single course of IVIG, treatment with an oral steroid (methylprednisolone, 40 mg) and CellCept (500 mg) was started. Approximately 2 weeks after her discharge (5–6 weeks after symptom onset), DF experienced intermittent episodes of drooling, perseverative speech, oromandibular dystonia (e.g. chewing motions), giddiness, and paranoia. She had no continued overt seizure activity. A post-acute neuropsychological evaluation was conducted 6 weeks after DF's discharge (approximately 11 weeks after symptom onset).

Behavior observations. During her post-acute evaluation, DF demonstrated pressured speech and marked impulsivity.

Neuropsychological functioning. Results of cognitive testing revealed overall intellectual functioning in the average range, with evenly developed verbal and visual-spatial skills. Assessment of academic performance and adaptive daily living skills was consistent with overall cognitive functioning. DF's performances on measures of fine motor dexterity, visual-motor integration, sustained attention, executive functioning (e.g. visual-motor sequencing and cognitive flexibility), and visual memory were age appropriate. Mild weaknesses (low average to impaired performances) in verbal memory and more substantial impairment (impaired to severely impaired performances) in problem-solving and language (e.g. confrontational naming and comprehension of instructions) were observed.

Evaluation in chronic phase

Interim history. Following her post-acute evaluation, both DF and her parents reported considerable improvement in cognitive functioning and noted that DF's personality, range

of emotions, sense of humor, and interpersonal interactions more closely resembled her premorbid functioning. DF was again independent with daily routines, was actively engaged with friends, and had returned to her hobbies and activities. Per her medical team's recommendations, DF returned to school part-time, then full-time. Six weeks after her post-acute evaluation, DF's daily oral steroid treatment was decreased to 30 mg. Approximately 3 months following her last discharge, DF reported no further neuropsychiatric events. She was working part-time, exercising regularly, and interviewing for college programs. A neuropsychological evaluation in the chronic phase (21 weeks after acute evaluation) was conducted. Approximately 2 weeks prior to her evaluation, DF began reporting some memory difficulties, which responded to an increase in her medication (i.e. oral steroid increased to 35 mg, CellCept increased to 500/1000 mg AM/PM). DF and her family reported no cognitive issues at the time of her evaluation in the chronic phase.

Behavior observations. During her evaluation in the chronic phase, DF exhibited mild word finding difficulty, as well as mild impulsivity and fidgetiness.

Neuropsychological functioning. Results of cognitive testing showed improved functioning overall. DF's performance on measures of visual reproduction, visual-motor sequencing and cognitive flexibility, verbal fluency, and verbal learning and retrieval was age appropriate and showed relative to significant improvement. Performance in other areas, including problem-solving, confrontational naming, comprehension of instructions, and verbal recognition, showed modest improvement but were still below average (borderline to impaired ranges).

Outcome

Eight weeks after DF's final evaluation, her daily oral steroid dosage was decreased to 25 mg. Just over 1 year after her last discharge, DF's daily oral steroid treatment had been weaned down to 3 mg and was completely tapered 3 weeks later. By that time, DF was reportedly doing well in a nursing program at a four-year university and experiencing no further symptoms. Despite DF's perception that she had returned to her baseline level of functioning, her most recent neuropsychological evaluation (chronic phase) would suggest some degree of persistent, subtle cognitive deficits in the areas of executive functioning (e.g. problem-solving), language (e.g. confrontational naming and comprehension of instructions), and memory (e.g. verbal recognition). DF's CellCept was decreased to 500 mg twice daily approximately 8 weeks after completion of her steroid taper, and all medications were discontinued 10 weeks after that (approximately 20 months after symptom onset).

Case 2 (BG)

Background

BG was an active and healthy 16-year-old, right-handed young woman with no reported previous psychiatric history or history of learning or attention problems. She was an average to above average high school student, earning mostly As and Bs, from a family of middle SES. Approximately 1 month before her admission to the hospital, BG experienced a generalized tonic-clonic seizure. Head CT and brain MRI conducted at that time were read as normal, while EEG showed intermittent slowing and epileptiform discharges over the bilateral temporal regions. BG was started on an AED, which was discontinued upon admission

to the hospital. One week after her seizure, BG began experiencing a progressive worsening of symptoms, including headaches, difficulty falling asleep, and problems with concentration, reading comprehension, remembering things, and homework completion. She started losing her appetite and gradually became more apathetic and lethargic. BG's verbal expression and writing ability declined. One week before her admission to the hospital, BG experienced difficulty formulating answers, exhibited nonsensical and perseverative speech, could no longer write, and began sleepwalking. She also had difficulty remembering events that occurred each day. On admission, BG presented with new onset right-hand weakness and rigidity and worsening expressive language. During her first 3 weeks in the hospital, BG had intermittent periods of worsening in her cognitive and neurological status with a fluctuating course of symptoms, including changes in mental status, difficulty with expressive language, flat affect, mild motor weakness (mainly on her right side), sleep difficulty, and loss of appetite. Lumbar puncture (LP) indicated abnormal findings in CSF with lymphocytic pleocytosis. Repeat brain MRI initially indicated possible iron deposition in the globus pallidus bilaterally, but further review suggested infection instead of iron deposition (see Figure 1). A pelvic ultrasound was read as normal. BG's CSF panel was confirmed positive for NMDAR antibodies, and immunotherapy with IV steroids and IVIG was initiated (4 weeks after symptom onset). A serum titer was also positive for NMDAR antibodies (1:20, reference range <1:10). Though glucose (50, reference range 45–80 mg/dL) was in the normal range, BG's CSF panel showed abnormally elevated levels of protein (51, reference range 15–45 mg/dL), lymphocytes (98, reference range 40–80), and total nucleated cells (44, reference range 0–5/uL). No information regarding oligoclonal bands or multiple sclerosis screening was available in BG's laboratory records. Five days after her admission, BG experienced a seizure, and AED therapy was restarted. She experienced a second seizure in the hospital 2 weeks later, and her AED dose was increased. Repeat EEG conducted 3 weeks after admission continued to show bihemispheric delta activity. BG's final EEG 4 days later showed right frontal, persistent high-amplitude beta activity. Prior to her discharge, an inpatient neuropsychological evaluation was conducted (see Table 2).

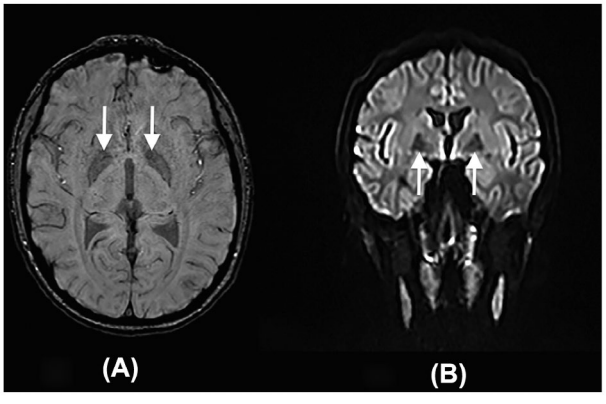

Figure 1. Axial SWI (Panel A) and coronal DWI (Panel B) images of patient BG's brain on admission at the level of the basal ganglia, showing symmetric slight signal dropout in the region of the globus pallidus. Note: This was initially read as indicative of iron deposition in these regions by neuro-radiology, though further review suggested possible infection.

Table 2. Summary of neuropsychological measures for case 2 (BG) at all evaluations.

Cognitive domain	Measure		Acute	Chronic
Intelligence:	WAIS-IV			
		SIM		(10)
		VOC		(11)
		BD		(13)
		MR		(11)
		DS		(7)
		ARITH		(8)
		SS		(9)
		CD		(6)
Motor/sensory:	Grooved Pegboard			
		DOM		83
		NDOM		78
Visual-spatial:	DTVMI		<45	104
Attention:	CPT-II			
		Omissions		T-47
		Commissions		T-68
Executive functioning:	DKEFS Trail Making Test			
		VS		(10)
		NS		(12)
		LS		(10)
		NLS		(9)
		MS		(9)
	DKEFS CWI			
		CN		(12)
		WR		(13)
	DKEFS Tower TAS			(10)
	SDMT (Oral)			98
Language:	DKEFS Verbal Fluency			
		LFTC		(8)
		CFTC		(10)
		CSTC		(10)
		CSTA		(10)
	BNT			87
	PPVT-4		20	103
Memory:	CVLT-II			
		Learning		T-41
		SD Recall		93
		LD Recall		85
		LD Recog.		100
Academic functioning:	WRAT-4			
		WR		116
		MC		102
		SP		117

Abbreviations: WAIS-IV: Wechsler Adult Intelligence Scales-IV; SIM: Similarities; VOC: Vocabulary; INFO: Information; BD: Block Design; MR: Matrix Reasoning; VP: Visual Puzzles; DS: Digit Span; ARITH: Arithmetic; SS: Symbol Search; CD: Coding; DOM: Dominant hand; NDOM: Nondominant hand; DTVP: Beery-Buktenica Developmental Test of Visual Perception; DTVMI: Beery-Buktenica Developmental Test of Visual-Motor Integration; JLO: Benton Judgment of Line Orientation; CPT-II: Conners Continuous Performance Test-II; TOL-DX: Tower of LondonDX-2; RCFT: Rey-Osterrieth Complex Figure Test; DKEFS: Delis-Kaplan Executive Functioning System; VS: Visual Scanning; NS: Number Sequencing; LS: Letter Sequencing; NLS: Number-Letter Sequencing; MS: Motor Speed; FDTC: Filled Dots Total Correct; EDOTC: Empty Dots Only Total Correct; STC: Switching Total Correct; CWI: Color-Word Interference; CN: Color Naming; WR: Word Reading; TAS: Total Achievement Score; LFTC: Letter Fluency Total Correct; CFTC: Category Fluency Total Correct; CSTC: Category Switching Total Correct; CSTA: Category Switching Total Accuracy; SDMT: Symbol Digit Modalities Test; MAE: Multilingual Aphasia Examination; COWA: Controlled Oral Word Association; SR: Sentence Repetition; BNT: Boston Naming Test; ICSOR: Iowa-Chapman Speed of Reading; PPVT-4: Peabody Picture Vocabulary Test-4; CVLT-II: California Verbal Learning Test-II; HVLT-R: Hopkins Verbal Learning Test-Revised; RAVLT: Rey Auditory Verbal Learning Test; SD: Short-Delay; LD: Long Delay; Recog.: Recognition; WMS-III/IV: Wechsler Memory Scales-III/IV; LM-I/II: Logical Memory-I/II; LMR: Logical Memory Recognition; VR-I/II: Visual Reproduction-I/II; VRR: Visual Reproduction Recognition; FWD: Forward; BKWD: Backward; BVRT: Benton Visual Retention Test; WRAT-4: Wide-Range Achievement Test-4; WR: Word Reading; MC: Math Computation; SP: Spelling; WJ-III: Woodcock-Johnson Tests of Achievement-III; LW: Letter-Word Identification; CA: Calculation; BDI-FS: Beck Depression Inventory Fast Screen; BDI-II: Beck Depression Inventory-II; BAI: Beck Anxiety Inventory; CDI-2: Children's Depression Inventory-2; RCMAS-2: Revised Children's

Manifest Anxiety Scale-2; Nml: Normal; d/c: discontinued; Sev: Severely; Imp: Impaired; Bdl: Borderline; Min: Minimal; and Sxs: Symptoms.
Scores: These scores indicate performance compared to other same-aged individuals. Standard scores have an average range of 85–115. Scaled scores (in parentheses) have an average range of 7–13. *T*-scores (*T*-#) have an average range of 40–60. Percentile ranks show how well an individual performed compared to a group of individuals of the same age. Scores are shaded to indicate level of impairment according to the following scale:

Average or better/normal performance
Low average performance
Borderline performance
Impaired performance
Severely impaired performance or discontinued task

Acute evaluation

Behavior observations. During her acute evaluation, BG was very disoriented and appeared to be in a state of delirium. She presented with flat affect, was echolalic, demonstrated tangential speech, and was highly distractible.

Neuropsychological functioning. Due to BG's impaired orientation and mental status, her severely impaired performance on measures of receptive vocabulary and visual-motor integration was considered invalid.

Evaluation in chronic phase

Interim history. After no improvement in symptoms following IV steroid and IVIG treatment, second-line treatment with rituximab and cyclophosphamide was initiated prior to BG's discharge. She was also started on oral prednisone. One day after initiating second-line treatments, BG experienced two seizures characterized by facial twitching, eye deviation, and tongue movements all to the right. As her seizures were not responsive to medical treatment, BG was put under sedation and transferred to the PICU for mechanical ventilation. She received a second course of rituximab and cyclophosphamide in the PICU 3 weeks later. BG was extubated to room air the next day but experienced mental confusion. In the following days, after receiving the second course of second-line treatment, BG's mental status was unstable. She communicated with others by pointing or using single words. Her gait was unsteady and required assistance with walking. BG was able to hold objects with her hands but was unable to feed herself. With intensive physical, occupational, and speech/language therapies, BG's symptoms gradually improved. She continued on oral prednisone and underwent a third course of rituximab and cyclophosphamide almost 4 weeks after her previous treatment. Upon discharge, BG was able to maintain spontaneous conversational speech with only intermittent confusion, perseveration, or speech blocks. She was able to comprehend simple, one- to two-sentence messages and spell three- to four-letter words accurately with multiple attempts. Upon discharge from the hospital (6 weeks after admission), BG's irritability and frustration gradually subsided. She experienced no further seizure episodes.

At the time of her evaluation in the chronic phase (14 weeks after acute evaluation and completion of second-line treatment), both BG and her mother reported a stable course of recovery and that BG was functioning close to her premorbid level. BG was working on online courses to prepare for her return to school for the fall semester 2 months later. She was actively engaged with friends and participating in social activities. BG reported experiencing mild concentration difficulty and slow processing speed, requiring more time to finish

academic tasks and read than she did before. BG also described ongoing mild hand tremors, especially when tasks involved fine motor coordination (e.g. handwriting). She expressed frustration with her prolonged recovery course and temporary activity restrictions. A neuropsychological evaluation in the chronic phase was conducted.

Behavior observations. During her evaluation in the chronic phase, BG was alert and oriented and exhibited appropriate affect, though some word finding difficulty and mild impulsivity were noted.

Neuropsychological functioning. Results of cognitive testing indicated overall average intellectual abilities with comparable performance on most other test measures, including visual-motor integration, receptive vocabulary, visual-motor sequencing, verbal fluency, rapid naming, and problem-solving skills. BG demonstrated relative weaknesses (low average to borderline ranges) in executive functioning, particularly inhibition and working memory, as well as retrieval-based verbal memory, confrontational naming, and fine motor dexterity bilaterally.

Outcome

Following her final evaluation, BG was switched to oral azathioprine (100 mg/daily), and repeated lab work indicated normal enzyme activity. Just over 1 year after her last discharge, BG continued on her oral azathioprine therapy (with plans to fully taper within 3 months), felt that she had returned to 100% of baseline, was doing well in high school, and was experiencing no further symptoms.

Case 3 (CK)

Background

CK was an 18-year-old, right-handed, bilingual (Spanish-speaking until age 5, primarily English-speaking thereafter) high school senior with no reported previous psychiatric history or history of learning or attention problems. She was an average to above average student from a family of middle SES at the time of her first ED admission for new onset seizure. She had a five-day viral prodrome with flu-like symptoms of low-grade fever, sore throat, body aches, and intractable vomiting, despite local treatment with ondansetron. CK was brought in by EMS after her mother witnessed generalized convulsions with respiratory alterations and tongue biting at home. This was followed by post-ictal confusion and another tonic-clonic seizure witnessed by ED staff. Electrolytes showed a metabolic lactic acidosis (lactic acid of 20 mEq/L, reference range .5–2.2 mEq/L) consistent with seizure. CK was admitted for a comprehensive workup for new-onset seizure, including MRI, LP, and EEG, all of which were unremarkable. She was started on AED therapy, with the medication being later changed due to increased anxiety symptoms. CK remained hospitalized for 4–5 days until her nausea and vomiting improved, and she was discharged home.

Over the next week, CK returned to the ED for worsening anxiety, agitation, and confusion. A psychiatric evaluation was conducted, and outpatient therapy for anxiety and depression was recommended. CK's mother continued to report behavioral decline, however, including insomnia, odd behaviors (e.g. taking off her clothing at inappropriate times and/or getting out of bed in the middle of the night to bathe), strange speech patterns, and intermittent

oral movements. CK was readmitted to the hospital approximately 2.5 weeks after the initial viral prodrome. Exam upon admission was consistent with delirium, showing decreased attention, poor clock drawing ability, and attention to apparent visual hallucinations (see Figure 2). Physical exam was notable for oral automatisms, stuttering speech, intermittent wandering hand movements, and increased psychomotor activity. Furthermore, CK was noted to have constant nocturnal movements and inability to sleep more than 20 min at a time. LP was repeated and, due to high clinical suspicion for anti-NMDA receptor encephalitis, CK was empirically started on IVIG (1 g/kg/daily) for 2 days followed by IV methylprednisolone (1 g/daily). Her AED was again switched after EEG showed concern for seizures. Repeat brain MRI showed subtle FLAIR signal increases in the bilateral hippocampi (see Figure 3). The next week, CK's CSF panel was confirmed positive for NMDAR antibodies. A serum titer was also positive for NMDAR antibodies (1:20, reference range <1:10). CK's CSF panel, however, showed protein (9, reference range 14–45 mg/dL), glucose (74, reference range 40–75 mg/dL), and total nucleated cells (3, reference range 0–3/mm3) to be within normal limits. A multiple sclerosis screen was also normal, and there was no evidence of oligoclonal bands or blood–brain barrier (BBB) dysfunction from CSF studies. A pelvic ultrasound was read as normal. She was discharged 13 days after her second admission with only mild improvement of insomnia, mildly improved attention, and resolution of visual hallucinations. CK's discharge treatment plan included outpatient IVIG (1 g/kg) every 4–6 weeks, oral prednisone (60 mg/daily) with a slow six-month taper (decrease of 10 mg/month), and close follow-up with neuropsychological examination planned for 4 days after discharge (see Table 3).

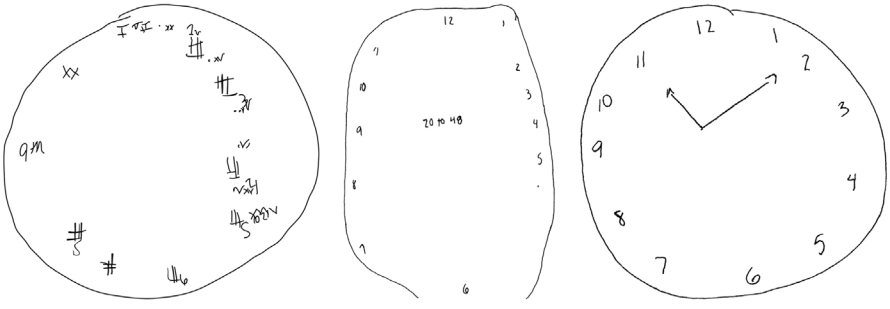

Figure 2. Clock drawings performed by patient CK. The patient was instructed to draw a clock face, put in all the numbers, and set the hands to show a specific time. Panel A: Clock drawn during patient CK's acute admission (approximately 3.5 weeks after the onset of her viral prodrome), contemporaneous with MRI in Figure 3, Panel A. There was an abnormal mixture of Arabic numerals, Roman numerals, letters, and symbols in place of the numbers 1–12. The patient was unable to set any hands to represent the time as 10 after 11. The performance was severely impaired and consistent with delirium. Panel B: Clock drawn during the first full neuropsychological assessment, 4 weeks and 1 day after that in Panel A, still during the acute period. Abnormal visual-spatial distortions are present, but the numbers are placed in correct sequence. The representation of time is severely impaired, with the phrase '20 to 48' instead of clock hands denoting 20 to 4. Panel C: Clock drawn in the post-acute period, 17 weeks and 3 days after that in Panel B. There is mild visual-spatial imprecision with the clock hands not meeting in the center of the face, but all other aspects are essentially normal. Of note, patient CK drew another clock (not pictured) as part of a Montreal Cognitive Assessment obtained at an outpatient neurology visit, 5 weeks after that in Panel B and 12 weeks before that in Panel C. That clock was mildly abnormal, with accurately sequenced but imprecisely spaced numbers along with reversed lengths of the hour and minute hands.

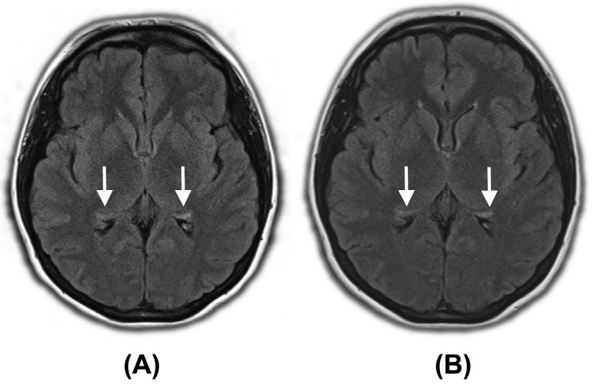

Figure 3. Panel A: An example slice from patient CK's MRI at day 1 of presentation, read as normal by neuro-radiology; however, on retrospect, possible subtle T2 FLAIR signal in the bilateral hippocampi was noted. Panel B: An example slice from patient CK's MRI 2 weeks after initial presentation; as per neuro-radiology, there is subtle high signal on FLAIR in the bilateral hippocampi. Although subtle, bilateral FLAIR T2 signal can be seen in anti-NMDA receptor encephalitis.

Acute evaluation

Behavior observations. During her acute evaluation, CK was cooperative but demonstrated extensive confusion. Severe impairments were noted in many areas of speech (e.g. word finding, fluency, and/or prosody), and frequent paraphasias and neologisms were noted. At times, CK was difficult to engage, as her voice would trail off and she would close her eyes and speak unintelligibly under her breath. Attention, comprehension, and thought processes were grossly impaired, and CK demonstrated apparent visual and auditory hallucinations. Mood was neutral with flat affect, although with occasional frustration over her impairments, becoming tearful at times and pushing a chair away from herself.

Neuropsychological functioning. CK demonstrated widespread and significant cognitive deficits (borderline to severely impaired ranges) across all assessed domains, as well as active hallucinations. She was oriented only to basic personal information and was only capable of completing the most basic of neuropsychological tests. Her presentation was seen as consistent with continuing delirium in the acute phase of anti-NMDA receptor encephalitis.

Post-acute evaluation

Interim history. About 2 days after her acute evaluation, CK showed a reversal of insomnia to hypersomnia (up to 18 h per day) followed by general normalization of sleep patterns. Against medical advice, she went on a multi-week trip out of the country. She was seen by a primary care physician and neurologist while abroad, was diagnosed with sinus tachycardia, and was started on a beta blocker. Sleep reportedly became fully normal during her time abroad. When CK returned to the U.S., she resumed high school classes but was not required to take final exams, and she graduated at the end of the year. A neurological exam at six-week follow-up indicated fully cleared delirium but some residual cognitive problems; CK's self-report was that all abnormal behaviors had remitted at that time. However, a month later (about 2.5 months post-hospitalization), CK stayed with a brother for several weeks. Her brother stated that, as children, they only spoke English to each other, but during the

Table 3. Summary of neuropsychological measures for case 3 (CK) at all evaluations.

Cognitive domain	Measure		Acute	Post-acute	Chronic
Orientation:		Time	Sev. Imp.	Nml.	Nml.
		Place	Bdl.	Nml.	Nml.
		Person	Nml.	Nml.	Nml.
Intelligence:	WAIS-IV				
		SIM		(9)	(8)
		VOC		(6)	(7)
		INFO		(9)	
		BD		(4)	(5)
		MR	(4)	(9)	(9)
		VP		(8)	
		DS	(1)	(10)	(9)
		ARITH		(6)	(9)
		SS		(10)	(13)
		CD		(10)	(13)
Motor/sensory:	Grooved Pegboard				
		DOM	46	79	61
		NDOM	49	88	70
Visual-spatial:	JLO			22%	11%
	Clock Drawing		Sev. Imp.	Nml.	
Executive functioning:	Trail Making Test				
		Part A	55	89	82
		Part B	d/c	107	85
	RCFT				
		Copy		T-44	T-30
		LD Recall		T-49	T-46
	Stroop Test				
		Word		T-36	T-37
		Color		T-44	T-44
		Color-Word		T-51	T-54
	DKEFS Tower				(8)
Language:	MAE				
		COWA	55	82	82
		SR		1–3%	1–3%
	BNT			T<20	T<20
	ICSOR			T-35	T-50
Memory:	HVLT-R/RAVLT		HVLT-R	RAVLT	RAVLT
		Learning	T<20	T-38	T-43
		SD Recall	T<20	T-40	T-43
		LD Recall	T<20	T-42	T-42
		LD Recog.	T<20	T-31	T-48
	WMS-III Spatial Span				
		FWD	(2)	(10)	
		BKWD	(2)	(12)	
	BVRT		d/c	T-40	T-40
Academic functioning:	WRAT-4				
		WR	74	80	
		MC		89	
Emotional functioning:	BDI-FS/BDI-II		Mild Sxs	Min. Sxs	Min. Sxs
	BAI			Mild Sxs	Min. Sxs

Abbreviations: WAIS-IV: Wechsler Adult Intelligence Scales-IV; SIM: Similarities; VOC: Vocabulary; INFO: Information; BD: Block Design; MR: Matrix Reasoning; VP: Visual Puzzles; DS: Digit Span; ARITH: Arithmetic; SS: Symbol Search; CD: Coding; DOM: Dominant hand; NDOM: Nondominant hand; DTVP: Beery-Buktenica Developmental Test of Visual Perception; DTVMI: Beery-Buktenica Developmental Test of Visual-Motor Integration; JLO: Benton Judgment of Line Orientation; CPT-II: Conners Continuous Performance Test-II; TOL-DX: Tower of LondonDX-2; RCFT: Rey-Osterrieth Complex Figure Test; DKEFS: Delis-Kaplan Executive Functioning System; VS: Visual Scanning; NS: Number Sequencing; LS: Letter Sequencing; NLS: Number-Letter Sequencing; MS: Motor Speed; FDTC: Filled Dots Total Correct; EDOTC: Empty Dots Only Total Correct; STC: Switching Total Correct; CWI: Color-Word Interference; CN: Color Naming; WR: Word Reading; TAS: Total Achievement Score; LFTC: Letter Fluency Total Correct; CFTC: Category Fluency Total Correct; CSTC: Category Switching Total Correct; CSTA: Category Switching Total Accuracy; SDMT: Symbol Digit Modalities Test; MAE: Multilingual Aphasia Examination; COWA: Controlled Oral Word Association; SR: Sentence Repetition; BNT: Boston Naming Test; ICSOR: Iowa-Chapman Speed of Reading; PPVT-4: Peabody Picture Vocabulary Test-4; CVLT-II: California Verbal Learning Test-II; HVLT-R: Hopkins Verbal Learning Test-Revised; RAVLT: Rey Auditory Verbal Learning Test; SD: Short-Delay; LD: Long Delay; Recog.: Recognition; WMS-III/IV: Wechsler Mem-

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Borderline performance
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Severely impaired performance or discontinued task

visit, CK would only speak to him in Spanish. He reported that, after a while, she switched back to speaking English to him, and after that he noted only occasional stuttering. AED and oral prednisone treatment continued, but IVIG infusions were discontinued due to acute respiratory side effects and rashes. In total, CK underwent five IVIG infusions, each 6 weeks apart. Repeat anti-NMDA titer in serum was normal (<1:10) at 4 months post-hospitalization. By that time, CK's daily oral steroid treatment had been tapered to 30 mg, with 2 months of taper remaining. The second outpatient neuropsychological exam took place 5 months after initial symptom onset, and 4 months after the first exam.

Behavior observations. CK had no recollection of the acute evaluation. Mood was neutral to mildly anxious, with mood-congruent (reserved or deferent) affect and behavior. Speech was mildly hypophonic but otherwise normal. Comprehension was intact. Thought processes were unremarkable. Effort was good during the exam, with some need for encouragement to continue trying or to take guesses.

Neuropsychological functioning. CK's cognitive performances were largely within the normal range and within expectations for her age and academic background. There were residual weakness (low average to severely impaired ranges) in language skills (naming, repetition, fluency, and speeded reading) and mild but variable weakness with speeded responding. Mild anxiety was present but not felt to be responsible for the residual cognitive weaknesses.

Evaluation in chronic phase

Interim history. CK was seen for a third outpatient neuropsychological exam just over 12 months after her acute evaluation. She had been tapered off prednisone by 6 months post-hospitalization. She had remained seizure free, and her AED was discontinued about 7 months post-hospitalization. The beta blocker had also been discontinued. CK had enrolled in a four-year university, reportedly earned average to above average grades, and felt that her academic performance was normal for her historical functioning. She had not required special academic accommodations. CK reported that anxiety concerns dissipated with the cessation of prednisone treatment. Sleep was described as normal.

Behavior observations. CK was polite and cooperative throughout the examination. Mood was euthymic, and affect was mood congruent. As with her prior exam, speech was mildly hypophonic but otherwise normal. Comprehension was intact. Thought processes were linear and goal directed. Effort and persistence were good.

Neuropsychological functioning. Results of testing showed evidence of some additional recovery of cognitive processing speed functions, with most other domains remaining stable. Some tests showed mild declines in performances, which appeared to be primarily due to a slight mismatch between her increased speed and her stable planning, reasoning, and self-monitoring abilities (i.e. sacrificing accuracy for speed). Difficulties in some language skills (e.g. naming, repetition, and/or fluency) were still present and wholly unchanged. CK's subjective sense was that her performances on such tests did not feel unusual or abnormally low for her, such that they represented baseline relative weaknesses rather than acquired deficits.

Outcome

Just over 13 months after her last discharge, CK was off all medications, was having no further symptoms, and was reportedly doing well in university coursework.

Discussion

Anti-NMDA receptor encephalitis is more readily recognized, accurately diagnosed, and effectively treated in a growing number of individuals. Nonetheless, the neuropsychological impact of anti-NMDA receptor encephalitis is less well understood. While there is a growing literature on neuropsychological outcomes of the condition, research has focused largely on adults, and the course of cognitive deficits from the acute to post-acute to chronic phase of the disease has not been well described.

Neuropsychological functioning was evaluated in our cohort of three adolescent females with anti-NMDA receptor encephalitis from their initial inpatient hospitalization to long-term follow-up (3.5–12 months after acute evaluation). While performance on cognitive testing during the acute phase varied considerably among the three young women, it was, not surprisingly, the most impaired of any of the evaluations. All three patients exhibited marked confusion at some point during the acute evaluation, and BG's scores were ultimately considered invalid due to her clear disorientation (delirium). This acute psychiatric presentation is believed to be a direct consequence of reversible NMDA receptor hypofunction (Hughes et al., 2010). While CK was able to complete more testing than BG, she was oriented only to basic personal information and could complete only the most basic of neuropsychological tests. DF exhibited the least impairment during her acute evaluation, though she was impulsive and perseverative on many tasks, consistent with previous findings of executive dysfunction in these patients. DF's attention was also poor and likely contributed to her impaired retrieval-based memory performance.

Both DF and CK underwent post-acute neuropsychological evaluations (6 and 20 weeks after acute evaluation, respectively). At the time of their post-acute evaluations, both patients continued on AED and oral steroid treatment, and DF also continued to receive IVIG infusions (CK's infusions had been discontinued due to adverse effects). While cognitive performances for both patients were largely within the normal range, DF continued to exhibit weaknesses

in verbal memory and problem-solving, and both patients demonstrated weaknesses in language skills. Naming deficits were observed in both patients, while DF also showed difficulty following instructions, and CK exhibited mild weaknesses in repetition, fluency, and speeded reading and responding.

All three patients underwent a final neuropsychological evaluation in the chronic phase (DF = 5 months after acute evaluation; BG = 3.5 months after acute evaluation; CK = 12 months after acute evaluation) and showed significant improvement in cognitive functions. All three patients and their families reported that the patients were at or near their premorbid level of cognitive functioning. DF and BG continued on AED and oral steroid treatment, while CK had been fully weaned from all medications. While all three patients demonstrated intact performances on many cognitive tasks, impairment was noted for some patients in the areas of fine motor dexterity, executive functioning, language, and memory. All three patients exhibited relative weaknesses in confrontational naming, while deficits in comprehension of instructions (DF) and repetition and fluency (CK) were also noted. As in other studies, some executive functioning difficulties were also observed, including problem-solving (DF), inhibition and working memory (BG), and planning and organizational skills (CK), though each patient also demonstrated other intact performances on executive tasks. Deficits in verbal memory were noted in both DF (recognition) and BG (retrieval-based memory), though, again, memory performances were not uniformly impaired and memory testing could not be performed with one patient (BG) during her acute evaluation to serve as a basis for comparison. Bilateral fine motor dexterity weakness was observed in both BG and CK.

While all three patients demonstrated clear improvement in cognitive functioning during the course of their recovery, results suggest that cognitive deficits may also persist in anti-NMDA receptor encephalitis. While the extant literature identifies executive functioning as an area of protracted impairment, selected deficits in fine motor dexterity, language, and memory were also observed at long-term follow-up in some of our patients. These deficits are, in part, consistent with prior work indicating disruption of synaptic processes in the hippocampus and its target areas, including the frontal lobe.

With regard to prognostic factors, none of the three patients had a detectable tumor and all received appropriate treatment fairly early in their disease course (between 2.5 and 4 weeks). BG was the only patient who required second-line treatment, as well as admission to an intensive care unit; she also underwent her last 'chronic' neuropsychological evaluation only 3.5 months following her acute evaluation. Nonetheless, her neuropsychological profile did not differ notably from the others in the chronic phase, as all three patients showed some mild cognitive deficits at follow-up.

Typically, when the BBB is interrupted by an inflammatory process, increases in inflammatory cells and/or protein are common. In CK's case, there was no evidence of inflammation or BBB disruption, which is unusual. The presence of CSF abnormalities for DF and BG, including elevations of lymphocytes, protein, and total nucleated cells, was not associated with worse neuropsychological functioning, though the decrease in CK's serum antibody titer between time of diagnosis and 4 months post-hospitalization was associated with improved cognition.

For each patient, there was an association between the presence and persistence of seizures and neuropsychological functioning. All three patients demonstrated general improvements on cognitive testing that coincided with receiving immunotherapy, improved EEG, and changes or dose increases of AED. The relationship between frequency and duration

of seizures and neuropsychological outcome was less clear, however, as each patient demonstrated mild deficits in at least three domains assessed at follow-up, and their cognitive profiles did not differ notably. Similarly, while the presence of delirium during each patient's acute evaluation was associated with marked neuropsychological impairment, the duration and severity of delirium did not appear predictive of neuropsychological outcome among the group.

It is also important to consider the role of the patients' developmental and psychosocial histories on neuropsychological outcome. Based on the information available, all three patients were reported to be relatively high-functioning individuals premorbidly. None had a reported psychiatric history or history of learning or attention problems, each was an average to above average student (based on high school grades and/or standardized test scores), the two patients who were not still in high school at long-term follow-up (DF and CK) were doing well at four-year universities while BG continued to do well in high school, and all were from either middle or upper middle SES backgrounds. It seems reasonable to suspect that these patients' generally favorable premorbid characteristics served as possible protective factors for neuropsychological outcome, given their much improved and largely intact cognitive abilities within 1 year of their acute evaluations. Though CK's subjective report was that her mild language deficits during the chronic phase of her evaluation likely represented baseline weaknesses rather than acquired deficits, which may be related, in part, to bilingualism, all three patients evidenced similar language difficulties at follow-up. The presence of these (and other) mild cognitive deficits in all three patients underlies the need for immediate and aggressive treatment, as well as repeat neuropsychological assessment to optimize neuropsychological outcomes in this population.

Neuropsychological follow-up is critical for individuals with anti-NMDA receptor encephalitis. Acutely, evaluations of cognitive functioning in the acute phase of the disease course assist the medical team with differential diagnosis. Regressions in cognition help differentiate between a psychiatric diagnosis and neurological involvement. The neuropsychological profile may be used to help corroborate results of certain aspects of the neurological workup, like EEG results, while CSF panels are pending. The data also demonstrate how severely impairing the disease has been to cognition, which will inform the recovery process. Conducting neuropsychological evaluations at multiple time points is necessary to help monitor disease activity following the acute phase, potentially inform treatment, and provide recommendations for reintegration into the patient's home, school, and community settings.

While there is not yet any standard guideline for scheduling testing, results of the current study, as well as other research in this area, highlight the importance of documenting cognitive deficits during the patient's acute phase (most often at the initial inpatient admission), as well as following the course of cognitive recovery after first-line treatment has been administered (post-acute phase; generally 2–6 months after symptom onset) and at long-term follow-up after most or all treatments have been discontinued and the patient returns to their premorbid activities (chronic phase; 6–24 months after symptom onset) (see Table 4). Given that some cognitive deficits in anti-NMDA receptor encephalitis have been found to persist upwards of 2 years after symptom onset, neuropsychological monitoring at least until this point is encouraged, especially if ongoing deficits are noted. Batteries that formally assess attention, executive functioning, language, and memory may be most sensitive to accurately identifying the most common cognitive sequelae seen in anti-NMDA receptor encephalitis. Given the possibility that patients may experience delirium, delusional

Table 4. Proposed schedule for neuropsychological testing throughout disease and recovery course.

Acute phase	Time of initial inpatient admission	Usually within 1 month of symptom onset
Post-acute phase	After administration of first-line treatment	2–6 months after symptom onset
Chronic phase	After most or all treatments have been discontinued and the patient returns to their premorbid activities	6–24 months after symptom onset; for patients showing persistent cognitive deficits in the chronic phase, neuropsychological follow-up for at least 24 months after symptom onset is encouraged

behavior, or overt psychosis, particularly during the acute phase of the disease, flexibility in conducting the initial neuropsychological evaluation to ensure adequate engagement of the patient and the collection of valid data is key. In the end, academic or professional accommodations may be warranted for patients in the chronic phase of anti-NMDA receptor encephalitis.

Taken together, our findings are consistent with most of the existing studies examining adults that found cognitive deficits following anti-NMDA receptor encephalitis. Our results also demonstrate gradual improvement in cognitive symptoms at multiple time points throughout the recovery course. Our three patients, as with the vast majority of those recovering from anti-NMDA receptor encephalitis, reported no difficulties during their final evaluation, despite each showing mild impairment in some areas of their cognitive functioning. While it is possible that some of these deficits might represent baseline relative weaknesses rather than acquired deficits, they may also reflect a potential self-reporting bias for underestimating or downplaying cognitive symptoms. An element of anosognosia cannot be entirely ruled out, but our clinical impressions across all cases were that, as in other patient populations like mild traumatic brain injury, the reports were more influenced by a determination to not be seen as disabled or impaired and to return to their premorbid levels of functioning as soon as possible. This underscores our proposal that neuropsychological assessment may be useful in detecting cognitive deficits of which pediatric patients with anti-NMDA receptor encephalitis are often unaware or unable or unwilling to acknowledge; thus, neuropsychological monitoring for at least 24 months after symptom onset is encouraged. Future studies that evaluate cognitive functioning in a larger pediatric sample at predetermined time points using a consistent set of neuropsychological measures are needed to further clarify long-term cognitive outcomes of anti-NMDA receptor encephalitis.

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Disclosure statement

No potential conflict of interest was reported by the authors.

References

Armangue, T., Petit-Pedrol, M., & Dalmau, J. (2012). Autoimmune encephalitis in children. *Journal of Child Neurology, 27*, 1460–1469.

Azizyan, A., Albrektson, J., Maya, M., Pressman, B., & Moser, F. (2014). Anti-NMDA encephalitis: An uncommon, autoimmune mediated form of encephalitis. *Neuroradiology, 8*, 1–6.
Bach, L. (2014). Long term rehabilitation management and outcome of anti-NMDA receptor encephalitis: Case reports. *NeuroRehabilitation, 35*, 863–875.
Chapman, M., & Vause, H. (2011). Anti-NMDA receptor encephalitis: Diagnosis, psychiatric presentation, and treatment. *American Journal of Psychiatry, 168*, 245–251.
Dalmau, J., Tüzün, E., Wu, H., Masjuan, J., Rossi, J., Voloschin, A., … Lynch, D. (2007). Paraneoplastic anti-N-methyl-D-aspartate receptor encephalitis associated with ovarian teratoma. *Annals of Neurology, 61*, 25–36.
Dalmau, J., Gleichman, A., Hughes, E., Rossi, J., Peng, X., Lai, M., … Lynch, D. (2008). Anti-NMDA-receptor encephalitis: Case series and analysis of the effects of antibodies. *The Lancet Neurology, 7*, 1091–1098.
Dalmau, J., Lancaster, E., Martinez-Hernandez, E., Rosenfeld, M., & Balice-Gordon, R. (2011). Clinical experience and laboratory investigations in patients with anti-NMDAR encephalitis. *The Lancet Neurology, 10*, 63–74.
Finke, C., Kopp, U., Prüss, H., Dalmau, J., Wandinger, K., & Ploner, C. (2012). Cognitive deficits following anti-NMDA receptor encephalitis. *Journal of Neurology, Neurosurgery, & Psychiatry, 83*, 195–198.
Finke, C., Kopp, U., Scheel, M., Pech, L., Soemmer, C., Schlichting, J., … Paul, F. (2012). Functional and structural brain changes in anti-N-methyl-D-aspartate receptor encephalitis. *Annals of Neurology, 74*, 284–296.
Finke, C., Kopp, U., Pajkert, A., Behrens, J., Leypoldt, F., Wuerfel, J., … Paul, F. (2016). Structural hippocampal damage following anti-N-methyl-D-aspartate receptor encephalitis. *Biological Psychiatry*, *79*, 727–734.
Gresa-Arribas, N., Titulaer, M., Torrents, A., Aguilar, E., McCracken, L., Leypoldt, F., … Dalmau, J. (2014). Antibody titres at diagnosis and during follow-up of anti-NMDA receptor encephalitis: A retrospective study. *Lancet Neurology, 13*, 167–177.
Guo, Y., Kuan, T., Hsieh, P., Lien, W., Chang, C., & Lin, Y. (2014). Rehabilitation for a child with recalcitrant anti-N-methyl-D-aspartate receptor encephalitis: Case report and literature review. *Neuropsychiatric Disease and Treatment, 10*, 2263–2267.
Hughes, E., Peng, X., Gleichman, A., Lai, M., Zhou, L., Tsou, R., … Balice-Gordon, R. (2010). Cellular and synaptic mechanisms of anti-NMDA receptor encephalitis. *Journal of Neuroscience, 30*, 5866–5875.
Iadisernia, E., Battaglia, F., Vanadia, E., Trapolino, E., Vincent, A., & Biancheri, R. (2012). Anti-N-Methyl-d-aspartate-receptor encephalitis: Cognitive profile in two children. *European Journal of Paediatric Neurology, 16*, 79–82.
Irani, S., Bera, K., Waters, P., Zuliani, L., Maxwell, S., Zandi, M., … Vincent, A. (2010). N-methyl-D-aspartate antibody encephalitis: Temporal progression of clinical and paraclinical observations in a predominantly non-paraneoplastic disorder of both sexes. *Brain, 133*, 1655–1667.
Keller, S., Roitman, P., Ben-Hur, T., Bonne, O., & Lotan, A. (2014). Anti-NMDA receptor encephalitis presenting as an acute psychotic episode in a young woman: An underdiagnosed yet treatable disorder. *Case Reports in Psychiatry, 2014*, 3 p. doi:http://dx.doi.org/10.1155/2014/868325.
Li, F., & Tzien, J. (2009). Memory and the NMDA receptors. *New England Journal of Medicine, 361*, 302–303.
Marcos-Arribas, L., Almonacid, J., & Dolado, A. (2013). Neuropsychological profile of anti-NMDA receptor encephalitis. *Psychology, 4*, 776–781.
Onur, O., Schlaepfer, T., Kukolja, J., Bauer, A., Jeung, H., Patin, A., … Hurlemann, R. (2012). The n-methyl-d-aspartate receptor co-agonist d-cycloserine facilitates declarative learning and hippocampal activity in humans. *Biological Psychiatry, 67*, 1205–1211.
Poloni, C., Korff, C., Ricotti, V., King, M., Perez, E., Mayor-Dubois, C., … Deonna, T. (2010). Severe childhood encephalopathy with dyskinesia and prolonged cognitive disturbances: Evidence for anti-N-methyl-D-aspartate receptor encephalitis. *Developmental Medicine & Child Neurology, 52*, 78–82.
Titulaer, M., McCracken, L., Gabilondo, I., Armangue, T., Glaser, C., Iizuka, T., … Dalmau, J. (2013). Treatment and prognostic factors for long-term outcome in patients with anti-NMDA receptor encephalitis: An observational cohort study. *The Lancet Neurology, 12*, 157–165.
Vahter, L., Kannel, K., Sorro, U., Jaakmees, H., Talvik, T., & Gross-Paju, K. (2014). Cognitive dysfunction during anti-NMDA-receptor encephalitis is present in early phase of the disease. *Oxford Medical Case Reports, 2014*, 74–76.