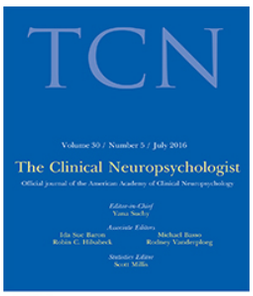

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Spontaneous recovery of memory functions in an untreated case of anti NMDAR encephalitis – a reason to maintain hope

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ABSTRACT

Objective: Anti N-methyl-D-aspartate receptor (anti-NMDAR) encephalitis is an autoimmune disorder that was only fully discovered recently and neuropsychological outcome data remains sparse. We present the case of BA, a 19-year-old male, which illustrates the cognitive outcome in an untreated case over a time period of over 2½ years. **Method:** We conducted three cognitive assessments, including tests of memory and executive functioning, over this time period and considered the evidence for reliable change in memory function using the Wechsler Advanced Clinical Solutions (ACS) serial assessment package. **Results:** Our findings revealed mild memory problems 6 months post-discharge with, at best, static and potentially declining memory functioning at follow-up assessment 12 months post-discharge. However, the results of testing at 30 months post-discharge revealed significant improvements in immediate and delayed memory index performances. **Conclusions:** Our report of a case of anti-NMDAR encephalitis provides evidence for spontaneous improvements in memory functioning occurring more than 2 years after initial assessment and also demonstrates both the utility and potential limitations of the ACS serial assessment software when used in a relatively typical clinical assessment situation.

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Anti-N-methyl-D-aspartate receptor; encephalitis; memory; assessment; recovery

Introduction

Anti N-methyl-D-aspartate receptor (anti-NMDAR) encephalitis

Anti N-methyl-D-aspartate receptor (anti-NMDAR) encephalitis is an autoimmune disorder that mainly affects young, female patients (Dalmau, Lancaster, Martinez-Hernandez, Rosenfeld, & Balice-Gordon, 2011). The condition is often associated with cancerous tumors, often found in the ovaries, although cases are also reported in the testes of males (Eker et al., 2008). This condition is considered the most common paraneoplastic encephalitis (Dalmau et al., 2011) and is caused by a patient's altered antibodies, which reduces surface NMDARs and leads to the reduction in NMDAR-related synaptic function. NMDA receptors are found throughout the brain but are concentrated in the hippocampus (Day, High, Cot, & Tang-Wai, 2011) and are thought to have specialist functions in terms of memory and learning (Kruse et al., 2014; Lo et al., 2010).

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Anti-NMDAR encephalitis has a number of distinct stages; prodromal, psychiatric, unresponsive, and hyperkinetic (Iizuka et al., 2008). Chapman and Vause (2011) summarized how the condition evolves over time. Initially, patients experience a short-lived flu-like illness. A psychotic phase follows, which often starts with anxiety or depression but progresses to severe behavioral and personality disturbance, delusions, paranoia, and hallucinations. It is not uncommon therefore for a primary psychiatric disorder to be mistakenly diagnosed. Unresponsiveness with hypoventilation, autonomic instability, and dyskinesias generally follows. The principal cognitive symptom is severe amnesia, which has been found to be associated with medial temporal atrophy on imaging (Martin-Mozon, Trujillo-Pozo, & Romero, 2012). The diagnosis often relies on the presence of specific autoantibodies to the N-methyl D-aspartate receptor being detected (Dalmau et al., 2011).

Authors in the field call for early identification of this condition, with clinicians being alert to a sudden decline in cognitive ability without delirium (Vahter et al., 2014). They also highlight the need for immediate and aggressive treatment, of which tumor resection and immunotherapy appear the most effective (Dalmau et al., 2007; Uchino et al., 2011). However, even with effective treatment, recovery appears slow and this has been attributed to treatments being unable to produce a rapid and sustained control over the immune response (Dalmau et al., 2008).

Most of the research involving anti-NMDAR encephalitis is in its infancy given that the condition was only fully discovered in 2007 (Dalmau et al., 2007). Research in the area is limited to a small number of case studies and case series with restricted neuropsychological data that indicate primary cognitive difficulties in memory and executive functioning (Dalmau et al., 2007; Finke et al., 2012; Lebon et al., 2012; Marcos-Arribas, Almonacid, & Dolado, 2013; Martin-Mozon et al., 2012; Vahter et al., 2014).

In terms of recovery, some authors report encouraging findings in terms of patients returning to normal cognitive functioning. Acién, Acién, Ruiz-Maciá, and Martín-Estefanía (2014) report that 80% of people with anti-NMDAR encephalitis and a detectable tumor recovered over a 3-month hospital stay. Dalmau et al. (2008) assessed recovery in terms of return to activity and Mini Mental State Examination (MMSE) score, upon which they report that 75% of 100 patients treated with tumor resection or immunotherapy, recovered or only had mild observable deficits in attention, planning, and impulsivity. This study was limited by the lack of more comprehensive neuropsychological assessment data. Further, a case study by Martin-Mozon et al. (2012) reported their patient completely recovered intellectual function after 6 years follow-up, which included intermittent memory rehabilitation. They concluded that cognitive dysfunction is transient and full recovery is possible over an extensive period of time. However, the authors determined change through higher test scores and changes in behavioral function, rather than by statistical analysis.

In contrast, continuing cognitive impairments have been found in other studies where more comprehensive neuropsychological testing has assessed outcome. Finke et al. (2012) studied nine patients with anti-NMDAR encephalitis, the majority of which had received immunotherapy treatment. At follow-up (median 43 months), impairments in memory and executive functioning remained in around 90% of patients. The most severe deficits were shown in patients with delayed or inefficient treatment. A further case reported by Vahter et al. (2014) also reported persistent memory problems in a patient, who received immunotherapy, after 12 months.

Hinkle et al. (2016) reported on three adolescent females with anti-NMDAR encephalitis, who all received anti-epileptic drugs and steroid treatment within a month of symptom onset. A flexible neuropsychological battery was completed that covered most cognitive and emotional domains. Testing took place at the acute stage (4–6 weeks after symptom onset), post-acute stage (2–6 months), and chronic stage (6–13 months). All three patients showed marked improvements in cognitive function, defined as a change of 2 or 3 standard deviations in testing, with subtle deficits remaining in language (i.e. naming, comprehension and fluency), executive function, fine motor skills, and memory. Interesting, each patient thought that their cognitive function had returned to their own baseline, which the authors felt highlighted the importance of repeated, detailed neuropsychological assessment. They recommended that testing continued beyond the 2-year mark if deficits are identified at the chronic stage.

A number of cases have claimed spontaneous recovery of anti-NMDAR encephalitis and associated cognitive impairment in patients that did not receive treatment. Evoli et al. (2012) found that their patient fully recovered (apart from a mild semantic fluency impairment) at 42 months follow-up and concluded that this may be a self-limiting condition. However, the patient in this case had not progressed to the late, severe stage of the illness. Furthermore, Iizuka et al. (2010) report that four Japanese women with the condition showed complete physical and cognitive recovery over three or more years, though further examination of this case series revealed that neuropsychological assessment was limited to an equivalent of the MMSE and patients had indeed received treatment in the form of antiviral medication, corticosteroids, immunotherapy, and antiepilepsy treatments during the course of their illness.

In summary, the current evidence appears to indicate that spontaneous recovery of neuropsychological functioning is less likely when no treatment has been provided or when the condition is severe. Additionally, the evidence for recovery is more limited when comprehensive neuropsychological evaluation is used to assess outcome rather than brief screening tools.

Serial assessment of cognitive functioning

Although single time-point assessments remain the mainstay of neuropsychological examinations, repeated assessments are a valuable, and in some cases common, approach to monitoring disease progression, recovery following neurological insult, or the impact of interventions. This is reflected in the recent American Academy of Clinical Neuropsychology policy paper that recommends neuropsychologists become more informed about the opportunities and challenges involved in serial assessment (Heilbronner et al., 2010).

Methods for assessing reliable change in test scores share the common logic that observed changes in test scores are likely the result of both true change (the actual improvement or decline in cognition function) and error resulting from confounding variance consequent to the tests themselves, the testing situation, and the person completing the tests. A number of approaches have been employed in the evaluation of reliable change. The reliable change model of Jacobson and Truax (1991) uses a scale's standard error of measurement and test–retest reliability to estimate the standard error of the differences. This method has been further developed (Chelune, Naugle, Luders, Sedlak, & Awad, 1993; Iverson, 2001) to include the mean practice effect. An alternative to these unidimensional methods is the use of

multiple regression-based formulas to predict scores at a second time point from time point 1 performance. Such formulas may also incorporate additional predictors, such as demographic variables, as well controlling for regression towards the mean. The Wechsler Advanced Clinical Solutions (ACS) package (Pearson Clinical Assessment, 2009) is one such solution, which provides clinicians with the ability to employ a standard regression-based model in order to evaluate change over 2 time points and works in conjunction with the existing Wechsler Adult Intelligence Scale (WAIS-IV) (Wechsler, 2008) and Wechsler Memory Scale (WMS-IV) (Wechsler, 2009) software package.

There has been little research into how cognitive function in adults changes over time after anti-NMDAR encephalitis. Most reported cases cover a short follow-up period, have limited neuropsychological data or do not measure improvement through statistical analysis. We present a case of NMDAR encephalitis where a comprehensive neuropsychological assessment was carried out at 3 time points (over 30 months) and reliable change was determined through regression analysis. The patient showed spontaneous recovery of memory function over time, despite not receiving any specific treatment for anti-NMDAR encephalitis. The apparent improvements observed in testing were assessed using regression-based change formulas derived from WMS-IV validation data and calculated using the Wechsler ACS software package.

Case study

BA was a 19-year-old Caucasian, right-handed male, previously healthy with no prior psychiatric history. He achieved normal developmental milestones. He was thought to be of average ability at school and went on to obtain a qualification in photography at college.

His initial symptoms began in December 2011 and included poor appetite, disturbed sleep, and having problems in interpersonal relationships. Depression was suspected and he was treated with anti-depressants by his GP. He then went onto to develop psychotic symptoms including thinking his parents were poisoning him and his older sister had possessed him. He was admitted to a psychiatric hospital in March 2012 and treated with anti-psychotic medication (Olanzapine) and Benzodiazepines. On the ward he was seen by an occupational therapist, physiotherapist, and a dietician, although his engagement with these professionals was minimal. An MRI brain scan and lumbar puncture were reported as normal.

BA was then transferred to a general hospital due to his physical health needs and his condition worsened, including exhibiting involuntary movements, seizures, mutism, and orofacial dyskinetic movements. His sleep functioning was severely compromised and Neuroleptic Malignant Syndrome (NMS) was suspected, as he had significantly raised CPK levels (1000–1500). He was transferred to a specialist tertiary neurosciences hospital in April 2012. His family was reluctant to start treatment for NMS so he was kept under observation and treated with IV fluids and fed through a nasogastric tube. Treatment at this stage was supportive and focused on improving diet and sleep. His MRI scan was normal and his EEG suggested diffuse non-specific encephalopathy, with no evidence of seizure syndrome. With supportive treatment his condition improved, with him then sleeping and eating to excess. He was discharged after 1 month.

Additional investigations revealed deranged liver function, fluctuating CPK levels, positive serology for Epstein-Barr virus, and positive monospot test suggested an infection 8 weeks previously. An HIV test was negative. No tumors were ever discovered, despite extensive investigations. His NMDA antibodies were found to be positive at the point of discharge and he was therefore diagnosed with anti-NMDAR encephalitis retrospectively. NMDA antibody levels were monitored over time and remained positive.

BA was assessed at 6 months (Time 1) and 12 months (Time 2) after inpatient discharge. He was re-referred for neuropsychological assessment as an outpatient at 30 months (Time 3) to clarify if his cognitive impairments had plateaued or improved.

Reported symptoms

At Time 1 and Time 2, BA and his mother reported problems with retrieving information and forgetting his way around in less familiar places. His memory problems were reported to have resolved at Time 3 and his mother felt he was 'back to normal'. By this time, he had completed a NVQ level 2 in care work with no difficulty and learnt to drive.

Neuropsychological assessment

Methodology

Cognitive assessment involved the administration of The Test of Pre-morbid Function (ToPF) (Wechsler, 2011), The Wechsler Memory Scales, 4th edition (WMS-IV) (Wechsler, 2009), two subtests (Trail Making Test and Verbal Fluency Test) from the Delis Kaplan Executive Function System Test (D-KEFS) (Delis, Kaplan, & Kramer, 2001) and the Hospital Anxiety and Depression Scale (HADS) (Zigmond & Snaith, 1983). The WMS-IV was administered at all three time-points as memory dysfunction was the main presenting neuropsychological symptom. In addition, subtests from the D-KEFS and the HADS were administered at Time 1 and 3. The ToPF was administered at Time 3. Table 1 indicates the tests completed at the three different time points. We hypothesized that, given the reported improvement in memory, there would be spontaneous recovery of memory function between Time 2 and 3. Therefore, the ACS package was used to examine reliable change in memory scores only.

Test behavior

When BA was seen for testing he was pleasant and cooperative. There were no specific concerns regarding his understanding or motivation to comply with the testing situation. At Time 1 and 2, he appeared fatigued in testing. He had insight into the fact that his performance had improved over time.

Table 1. Tests administered at separate time points.

Test administered	
Time 1 (6 months)	ToPF, WMS-IV, D-KEFS Trail Making Test, D-KEFS Verbal Fluency, HADS
Time 2 (12 months)	WMS-IV
Time 3 (30 months)	WMS-IV, D-KEFS Trail Making Test, D-KEFS Verbal Fluency, HADS

Test of Pre-morbid Functioning (ToPF), Wechsler Memory Scales, 4th edition (WMS-IV), Delis–Kaplan Executive Function System (D-KEFS), Trail Making Test and Verbal Fluency Test, Hospital Anxiety and Depression Scale (HADS).

Test results

A ToPF (Wechsler, 2011) was completed and supported the view that he had an average pre-morbid IQ (estimated IQ = 100).

Memory

The serial assessment memory scores are reported in Table 2. BA's auditory memory index (AMI) was assessed to be in the low average range at Time 1 and 2. However, this did not reflect the expected improvement in auditory memory scores as part of a serial assessment. Using the ACS serial assessment methodology, his obtained AMI score at Time 2 was significantly lower than predicted ($p \leq .05$). By Time 3, his AMI score had increased to the average range, however, as this was comparable to his predicted score based on the obtained Time 2 score, this was not deemed to be a statistically significant change.

His scores for Visual Memory showed greater variability as he scored in the average range at baseline (Time 1) and the low average range at Time 2. However, this index had improved to the high average range by Time 3. The improvement at Time 3 compared to his predicted score based on his Time 2 attainment was statistically significant, with the base rate of this difference being at the <1st percentile.

BA's immediate memory score at Time 1 was in the average range but dropped to the low average range at Time 2, with his Time 2 score being significantly lower than predicted. Examination of his subtest scores revealed that several of these were lower at Time 2 than Time 1. The immediate recall conditions of the auditory memory subtests were both significantly less at Time 2 than predicted by his Time 1 scores. At Time 3, the Immediate Memory Index had returned to the average range and was significantly higher than predicted by his Time 2 index, the base rate of difference being at the 1st percentile. BA scored higher on all of the immediate recall subtests at Time 3 compared to Time 2; however, the Designs I subtest

Table 2. Serial assessment of memory functioning.

	Initial assessment (Time 1)	Follow up (Time 2)			Follow up (Time 3)		
Index/test	Obtained score	Predicted score	Obtained score	Base rate (%)	Predicted score	Obtained score	Base rate (%)
AMI	88	100	84*	2–5	97	100	–
VMI	92	91	86	–	86	113*	<1
VWMI	80	89	83	–	91	88	–
IMI	94	96	84*	–10	89	107*	1
DMI	82	89	81	–	88	108*	1
	Scaled score						
LM I	9	11	7*	5	10	10	–
LM II	6	9	7	–	10	10	–
VPA I	9	12	7*	–1	10	10	–
VPA II	8	9	8	–	9	10	–
DE I	9	10	8	–	9	13*	5
DE II	9	8	7	–	7	10	–
VR I	10	10	9	–	9	11	–
VR II	7	9	7*	25	9	15*	1
SA	5	7	6	–	8	5*	10
SSP	8	9	8	–	9	11	–

Notes: Index scores are provided for WMS-IV indexes (mean = 100, *SD* = 15). Scaled scores are provided for WMS-IV subtests (mean = 10, *SD* = 3). Predicted scores are based upon obtained test scores at the previous administration.
*$p \leq .05$ compared to predicted score.

was the only immediate recall condition to significantly improve at Time 3 compared to predicted scores according to the ACS calculations.

His Delayed Memory Index scores did not demonstrate a significant improvement between Time 1 and 2. At Time 3, the Delayed Memory Index had improved to the average range and was significantly higher than predicted by his Time 2 index, with the base rate of difference being at the 1st percentile. BA scored higher on all the delayed recall subtests at Time 3 compared to Time 2; however, Visual Reproduction II was the only delayed recall condition to show significant improvement compared to the predicted scores given by the ACS calculations.

His scores for Visual Working Memory remained largely unchanged at all three time points, remaining in the low average range. However, his index scores showed steady increases, with the exception of his Spatial Addition score at Time 3 which was significantly lower than predicted and adversely affected his index score.

Executive functioning

Two subtests of the D-KEFS were completed at Time 1 and 3 (see Table 3 for an overview of additional assessments). In the Trail Making test at Time 1, BA scored in the average range across all 5 subtests (Visual Scanning, Letter Sequencing, Number Sequencing, Letter-Number Sequencing and Motor Speed). There was more variability in his scores at Time 3 as he scored in the average range for Visual Scanning and Number–Letter Sequencing, the borderline range for Number Sequencing, and the high average range for Letter Sequencing and Motor Speed. The number of errors made on the Number–Letter Sequencing task was in the average range. In summary, his performance on the Trail Making Test remained largely static and overall was not strongly suggestive of underlying executive dysfunction.

The Verbal Fluency test was also performed at Time 1 and 3. Letter Fluency at Time 1 was in the low average range but showed improvement to the average range at Time 3. His Category Fluency scores remained in the average range for both time points. However, he appeared to have more difficulty with the Category Switching task. At Time 1, he scored in

Table 3. Serial assessment of mood and executive functioning.

	Time 1		Time 3	
	Scaled score	Percentile	Scaled score	Percentile
D-KEFS Trail Making Test				
Visual scanning	9	37	9	37
Number sequencing	12	75	5	5
Letter sequencing	8	25	12	75
Number letter sequencing	10	50	10	50
Motor speed	12	75	12	75
D-KEFS Verbal Fluency Test				
Letter fluency	6	9	8	25
Category fluency	7	16	8	25
Category switching	6	9	5	5
Category switching accuracy	7	16	6	9
Hospital Anxiety and Depression Scale (HADS)	Raw score	Interpretation	Raw score	Interpretation
Anxiety	4	Normal	3	Normal
Depression	1	Normal	1	Normal

Delis–Kaplan Executive Function System (D-KEFS).
Scaled scores are provided for D-KEFS subtests (mean = 10, *SD* = 3).

the low average range for number of responses and the average range for switching accuracy. At Time 3, he scored in the borderline range for number of responses and the low average range for switching accuracy. The number of errors made on the fluency tasks was in the average range. This could indicate improvement in his verbal fluency scores and that his category fluency remained intact. However, his performance appeared confounded when a switching element was introduced.

Mood

BAs mood was assessed by the HADS at Time 1 and 3. His scores for anxiety and depression consistently resided in the normal range.

Discussion

We report neuropsychological assessment and serial cognitive testing of memory function in an untreated case of Anti-NMDAR encephalitis. Our findings revealed mild memory problems 6 months post-discharge with, at best, static and potentially declining memory functioning at follow-up assessment 12 months post-discharge. However, the results of testing at 30 months post-discharge revealed significant improvements in immediate and delayed memory index performances on the WMS-IV with a very low base rate of this degree of difference expected to occur in the general population. Therefore, testing over 2½ years post-discharge revealed evidence of spontaneous recovery in BA's memory functioning.

We considered issues relevant to the assessment of change in test scores over time, specifically the practice effects on the WMS-IV and the regression calculations embodied within the ACS package. A key aspect of determining reliable change is test stability, commonly referred to as test–retest reliability. Practice effects have received substantial attention in terms of their influence on test–retest reliability, with effects lasting up to 7 years documented (Salthouse, Schroeder, & Ferrer, 2004), while shorter retest intervals have been associated with greater effect sizes and longer test–retest intervals associated with lower correlations (Duff et al., 2010). Test–retest data for the WMS-IV used in the serial assessment calculations in the ACS package are based on retest data obtained for an interval of 14–84 days (mean 23 days) (Pearson Clinical Assessment, 2009). For the purpose of a serial assessment such as ours, with intervals of 223 and 525 days, the regression-based change model still employs the standard interval data as a basis for calculations. Subsequently, it is possible that the test–retest correlations used in the ACS regression model may be optimistically favorable when considering many of the typical repeat testing scenarios encountered in clinical practice, such as ours, where patient follow-ups are conducted many months and even years apart.

As the normative population on which the WMS-IV test–retest data underpinning the ACS serial assessment calculations comprised healthy examinee data, a further limitation exists in the ability to extrapolate practice effects from a healthy population to a clinical sample. Differences in the degree of practice effects between clinical and non-clinical samples have been observed, even in the absence of significant broader memory impairments on cognitive tasks (Baker, Taylor, & Aldenkamp, 2011). This introduces the possibility that expected practice effects derived from persons with normal memory functioning might over-estimate the degree of practice effect expected in an individual with underlying memory impairment.

Another issue of relevance to our serial assessment is that practice effects are typically reported to be largest between the first and second administrations, with small to negligible increases on further administrations (Ivnik et al., 1999), that have also been demonstrated in clinical populations in the early stages of recovery (Rawlings & Crewe, 1992). As the regression model in the ACS package does not account for changes in practice effects beyond the first and second administrations, it remains possible that the results obtained from our third assessment of BA underestimate the magnitude of the observed improvement.

A clinical conundrum in our formulation resulted from the finding that, despite a 16 index point increase in BA's AMI between T2 and T3, this was not found to be a statistically significant improvement in memory scores according to the ACS serial assessment calculation. The observed AMI change between T1 and T3 was in fact very similar to the change in score that was predicted from T1 to T2. In BA's case, we might expect that the practice effect would not be as substantial as the ACS package predicted between T2 and T3 as we would expect smaller practice effects to be occurring by the third administration. From a clinical perspective, we also considered it important to acknowledge the self-reported improvements in memory being made at T3. As such, it appeared that looking only for the presence of statistical significance in the change scores for the T2–T3 comparison would seem to ignore the broader improvements in memory test scores observed in this assessment and the patient's perception of improvement. We believe that this example supports the view of Iverson and Schatz (2015), who have noted that rigid application of reliable change approaches is likely to result in a failure to identify change in some people and that reliable change estimates should supplement, and not replace, clinical judgment.

It is interesting to consider the mechanism behind BA's recovery. There were clinical features that indicated the condition did not reach a critical stage for him including the fact he did not require intubating and imaging did not reveal any obvious atrophy. Other researchers have questioned why some people recover well from the condition. Iizuka et al. (2010) concluded that the condition results in functional rather than structural neuronal damage and therefore recovery is possible. They further suggest that recovery could be related to pharmacological effects, synaptic plasticity, or brain remodeling. A number of researchers have also indicated that brain atrophy after anti-NMDAR encephalitis can be reversible (Iizuka et al., 2010; Taguchi, Takashima, Nukui, & Tanaka, 2011). Taguchi et al. (2011) proposed that temporal brain shrinkage could be caused by long-term anesthetic agents and the immune responses of the anti-NMDAR encephalitis. Given that abnormal antibodies tend to decrease over time it may be that the immune response is not maintained.

AB's cerebral spinal fluid was monitored post-illness and although the antibodies reduced, it was still not considered to be in the normal range. However, this could indicate a trend towards normal antibody composition which might be relevant in explaining his gradual recovery. Given that no tumor was found, he may be at greater risk of relapse, which stands at about 25% (Dalmau et al., 2008). It has been suggested that patients receive immunosuppression treatment for 12 months to reduce the risk of relapse (Young et al., 2013). Additionally, his initial episode should mean that the condition would be identified and treated quickly if it re-occurred in the future.

One potential limitation to this case study is that no formal assessment of effort was used to evaluate performance validity. However, there was no indication of secondary gain and most of BA's scores were in the average range, which was not suggestive of widespread underperformance. He additionally scored above suggested cut-offs for suboptimal effort

on the Spatial Addition and Symbol Span task (Bouman, Hendriksm, Schmand, Kessels, & Aldenkamp, 2016; Young, Caron, Baughman, & Sawyer, 2012). A further limitation is the smaller number of cognitive assessments completed at Time 1 and 2. This occurred due to the demands of the clinical setting and due to memory function being the focus of the assessment.

In summary, our data supports a view that cognitive recovery from anti-NMDAR encephalitis is possible but may occur over an extended period. Therefore, long-term monitoring, rehabilitation, and cautious hope are recommended in these cases. From an assessment methodology perspective, the use of reliable change calculations in serial cognitive assessment can provide useful empirical validation of perceived differences in test scores over time and inform neuropsychological formulations. In our view, the ACS package provided a relatively sophisticated approach to reliable change assessment fronted by a user-friendly interface. Use of the ACS package may be limited in clinical practice, when assessments take place over more than two occasions and when follow-up cognitive testing spans larger test–retest intervals than those from which the regression model of the ACS is derived. These additional considerations highlight a need for the collation of test–retest data over more clinically relevant timescales and assessment scenarios involving larger numbers of follow-up administrations. We also consider that the scale of first to second administration practice effects on some tests highlights the need for alternative test stimuli on memory tests to be considered alongside the continued development of clinically useful reliable change assessment tools.

Disclosure statement

No potential conflict of interest was reported by the authors.

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