

The effects of immunologic brainstem encephalopathy on cognitive function following awakening from a progressive autoimmune coma

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We describe a unique patient who experienced a progressive autoimmune coma from age 14 to 17. The patient awoke after treatment with immunosuppressant medication. Although alertness, verbalization, and mobilization markedly improved, the patient reported persistent cognitive difficulties. Neuropsychological assessment from age 21 showed impairments in selective attention, distractibility, and memory. Conversely, higher-order executive functions were preserved. Electrophysiological analysis also identified abnormal neural signatures of selective attention. Eighteen months after the neuropsychological assessment, voxel-based morphometry revealed reduced white matter in the medulla compared to controls. The findings are discussed in terms of the impact of brainstem encephalopathy on cognitive mechanisms.

Keywords: Autoimmune coma; RAS (reticular activating system); Attention.

INTRODUCTION

There is a modest, but significant body of work reporting that deficits to isolated brainstem regions can produce cognitive impairments of the kind that are more typical of cerebral hemispheric damage (Garrard et al., 2002; Hoffman & Cases, 2008; Hoffman & Schmitt, 2004; Omar et al., 2007). These findings suggest a form of diaschisis or neurotransmitter depletion in which cognition is compromised through damage to subcortical regions that are distal from the cortical circuitry responsible for exercising cognitive control. In these patients attention and executive dysfunctions are commonly described, followed by memory disturbances. Until

now, motor recovery has been the focus of rehabilitation after brainstem damage; however it is becoming evident that cognitive dysfunction can persist and cause long-term functional impairments that should be treated as well (Omar et al., 2007).

The mechanisms underpinning brainstem-cortical interactions with respect to cognitive processes are not fully understood. Garrard et al. (2002) reported that the functional impairments seen across seven different patients with isolated brainstem damage did not appear related to any particular lesion site in the brainstem. Nevertheless, all patients had impairments of attention in common. In a larger group of patients with isolated brainstem or cerebellum lesions

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(Hoffman & Schmitt, 2004), it was reported that 47% showed impairment on executive tasks and 40% exhibited delayed memory problems (see also Hoffmann & Cases, 2008).

The occurrence of cognitive impairments in the context of heterogeneous lesions to different brainstem regions suggests that selective disruption at every anatomic level of the reticular activating system (RAS) may account for these neuropsychological impairments. The RAS provides a key regulatory influence over arousal-attention mechanisms through changes to the excitability of the cortex. The RAS comprises of a set of nuclei extending from the spinal cord to the inhibitory nuclei within the thalamus (Moruzzi & Magoun, 1949; Steriade, 1996). Long ascending sensory tracts travel from the spinal cord and form secondary branches to nuclei of the RAS. Additionally, collateral branches from auditory, visual, and olfactory pathways innervate the RAS nuclei. Excitatory signals via these pathways enhance synaptic transmission in the RAS in response to sensory input (Edlow et al., 2012; Moruzzi & Magoun, 1949; Steriade, 1996). Within the RAS, the midbrain reticular formation (MRF) has a role in enhancing sensory transmission during states of vigilance. It has been demonstrated that regional cerebral blood flow (rCBF) to MRF areas and the thalamic intralaminar nuclei was greater in the transition from relaxed wakefulness to an attention-demanding reaction-time task in human participants (Kinomura, Larsson, Gulyas, & Roland 1996).

The MRF sends projections to the thalamic intralaminar nuclei, which in turn, forms connections with the reticular complex of the thalamus. It has been proposed that the reticular complex serves a key role in guiding *selective* attention through gating neural transmission to cortical targets (Crick, 1984; Newman, 1995). Rapid bursts of firing from subpopulations of thalamic reticular neurons and subsequent inhibitory output from GABAergic neurons mediate the disengagement and subsequent deployment of attention. Increased neural spike activity from thalamic reticular neurons in monkeys during shifts of attention (McAlonan, Cavanaugh, & Wurtz, 2006) has provided the first evidence to support this idea of a flexible gating mechanism mediated by the reticular complex.

However, the gating mechanism of the reticular complex is under opposing influences from different systems. First, the MRF in the core of the brainstem can inhibit the gating of the

thalamic reticular neurons and enhance sensory transmission based on increased reactivity to novel or salient environment stimuli (Steriade, Dossi, Pare, & Oakson, 1991). Second, top-down prefrontal pathways are capable of inhibiting a selection made by the reticular neurons in response to a modification or change in ongoing goal-directed behavior. For instance, functional imaging has revealed a fronto-parietal-thalamic-brainstem network is associated with heightened states of vigilance when participants respond in unwarned situations compared to when they are given warning cues to respond to upcoming target stimuli (Mottaghy et al., 2006; Sturm et al., 2011). While progress has been made delineating prefrontal control mechanisms that exert top-down control within this network, less is known about modulatory influences within the brainstem.

The purpose of the current case study was to investigate a rare patient who had experienced immunologic brainstem encephalopathy, and subsequently presented with unusual cognitive impairments. The patient reported everyday problems with mental fatigue, paying attention in the context of distracting information, and difficulties with remembering the names of new acquaintances and the details of prior conversations. To quantify the frequency of these problems, we administered questionnaires to gauge the propensity for attention and memory errors in everyday situations.

A bespoke neuropsychological battery was designed to measure dissociable types of attention (sustained attention, selective attention, and attentional switching), memory (working memory, recall, forgetting speed, retroactive and proactive interference), and executive control (retrieval fluency, inhibitory control, and divided attention). We hypothesized that the neuropsychological profile of the patient would be universally impaired relative to controls, if brainstem encephalopathy caused global dysfunction of regulatory arousal. However, a more specific impairment of *selectivity* aspects of cognition with preservation of higher-order cognition might be expected if encephalopathy had affected interactions between the midbrain reticular formation and the thalamus, and disrupted the above-mentioned gating mechanism.

CASE HISTORY

We investigated a 21-year-old right-handed male with 15 years of formal education that was referred

to the Dublin Neurological Institute at the Mater Misericordiae University Hospital when he was 17-year old, with an 8-year history of progressive psychomotor deterioration. This deterioration initially began as muscle aches and pains, generalized fatigue, poor appetite, constipation, excessive perspiration, and subsequently progressed to a gradual behavioral change with decreased responsiveness. The patient lives with his parents and three siblings. His mother was diagnosed with multiple sclerosis when the patient was 10 years old; otherwise there was no family history of neurological disease. There was no history of alcohol or recreational drug use.

The patient reached normal developmental milestones, but first came to medical attention at the age of 5 when he presented to his family doctor with constipation and poor appetite. From 7- to 9-years old, he had a chronic sore throat and described difficulty sleeping. By 10 years of age, he was noted to have decreased initiative and interest. At the age of 11, he stopped attending school due to severe fatigue. By the age of 12, he was describing generalized joint pains, muscle weakness, and lethargy. At this time, he was referred to a physiotherapist and he was assessed by a psychiatrist who prescribed fluoxetine. Neither of these interventions ameliorated his symptoms. Symptoms of psychomotor regression progressed between the age of 12 and 14 years old, with associated weight loss (approximately 20 kg in 12 months) and marked shoulder and leg pain. At the age of 14 years, he was admitted for a 4-month period under pediatric and psychiatric services at a district general hospital, and was subsequently treated for presumed psychotic depression with citalopram and risperidone. Despite this, his symptoms continued to deteriorate considerably. From 14 to 17 years of age he stopped verbalizing, became immobile, and was incontinent of urine and feces. He required family prompting to swallow pureed foods. His level of alertness varied, and although predominantly mute and akinetic, at times he smiled at family jokes, appeared to watch television and drank from vessels placed in front of him. At this stage, the family commented on the emergence of persistent excessive perspiration and intermittent muscle jerks.

The patient was initially assessed at the Dublin Neurological Institute at the Mater Misericordiae University Hospital at the age of 17. He was lying on a trolley unresponsive with eyes closed and mouth open. He had upper and lower limb myoclonus, with occasional right versive head movements due to sternocleidomastoid myoclonus. He was noted to have spontaneous unpredictable

multidirectional conjugate eye movements consistent with opsoclonus. Muscular tone was flaccid throughout. There were no voluntary limb movements and minimal withdrawal responses to painful stimuli. Otherwise, there were no focal neurological signs and general physical examination was unremarkable. Electroencephalography (EEG) revealed no periodic or epileptiform abnormalities, however there was an excess of rhythmic activity in the alpha range, suggesting the possibility of an alpha coma. Standard cerebral magnetic resonance imaging (MRI) was unremarkable. Initial cerebrospinal fluid (CSF) examination was normal, but a subsequent CSF whilst on immunosuppressant therapy showed raised CSF protein (=1.64 g/L). Extensive screening investigations for inherited/degenerative, endocrine, metabolic, infective, and autoimmune causes of psychomotor regression were normal or negative.

Initial whole body positron emission tomography (PET) and computerized tomography (CT) imaging were reported as normal; however a subsequent CT thorax on immunotherapy showed an enlarged thymus. The patient underwent a thymectomy and histologic evaluation showed thymic hyperplasia. Given the presence of an opsoclonus-myoclonus syndrome, and exclusion of other potential etiologies, there was a high index of suspicion that an immunologic process was underlying his encephalopathy. A course of intravenous immunoglobulin was administered, followed by oral prednisolone 60 mg daily. Within days of commencing therapy, the patient was noted to be more alert. Within weeks, he began to verbalize appropriately and mobilize with a frame. The previously documented opsoclonus-myoclonus became less pronounced and ultimately disappeared. Despite this increase in alertness, the patient reported cognitive abnormalities, including specific attention and memory problems.

He described difficulties with attention in the context of distracting information. For example, trying to focus on one conversation in a busy room of concurrent background chatter. He also complained about everyday memory difficulties, particularly remembering new information, such as the names of new acquaintances and phone numbers. Although he reported recalling the gist of conversations or places, he complained of failing to remember essential information. Conversely, he also reported that unimportant details would sometimes be a source of perseveration in memory.

The patient's reported difficulties were corroborated by his high score on the Cognitive

TABLE 1
The patient's scales and questionnaires' scores

Scale/Questionnaire	Patient's score	Normal score
Cognitive Failures Questionnaire (CFQ)	68*	36.65 (9.41) ^a
Attention-Related Cognitive Errors Questionnaire (ARCEQ)	42*	33.37 (7.82) ^a
Everyday Memory Failures Questionnaire (EMFQ)	57*	34.11 (8.04) ^a
General Health Questionnaire (GHQ)	21	23/24
Beck Depression Inventory (BDI-II)	1	0–13 (minimal level)
Beck Anxiety Inventory (BAI)	1	0–7 (minimal level)

*Impaired score. ^aValues are mean (SD)

Failures Questionnaire (CFQ—Broadbent, Copper, FitzGerald, & Parkers, 1982), the Attention-Related Cognitive Errors Questionnaire (ARCEQ—adapted from Cheyne, Carriere, & Smilek, 2006), and the Everyday Memory Failures Questionnaire (EMFQ—adapted from Cheyn et al., 2006) (Table 1).

These questionnaires measure reported lapses in attention, memory, and absentmindedness experienced in everyday life. The patient's ratings clearly indicate difficulties in attention and memory. None of the items in the three scales was rated as "Never". In the CFQ, the patient rated 16 items out of 25 as occurring either "Very often" or "Quite often". Nine items only were rated as "Occasionally" or "Rarely". An example of item that the patient rated as occurring "Very often" is: "I daydream when I ought to be listening to something". The patient rated that 6 out of 12 items of the ARCEQ occur "Often" or "Very often". An example of items rated with the highest frequency in the ARCEQ is: "I start doing one thing at home and I get distracted into doing something else unintentionally". In the EMFQ, he rated that eight items out of fifteen occur "Often" or "Very often". Examples of items of the EMFQ occurring very often are: "I have lost track of a conversation because I zoned out when someone else as talking" and "When reading I find that I have read several paragraphs without being able to recall what I read". As a result of persistent attention and memory problems that patient was referred for further neuropsychological investigation at the age of 21. Eighteen months later, Voxel-based morphometry (VBM) was conducted

as described below in the methods. The patient was on azathioprine 100 mg twice daily while assessed. He has been on that dose since 2006.

METHODS

Procedures

The patient attended Trinity College Institute of Neuroscience three times for assessment. At his first assessment, he was 21-years old. The first session involved a neuropsychological assessment and electroencephalographic (EEG) recordings during a three-stimulus oddball paradigm (date: 16 October 2009). Healthy participants were assessed using the same EEG procedure. The second session involved a more comprehensive assessment of everyday attention and was delayed (date: 12 October 2010) due to the patient being unable to travel for assessment due to hip pain and discomfort, and excessive fatigue. Finally, the patient underwent an MRI assessment (date: 19 April 2012). During the MRI assessment, the patient was asked to lie in the MRI scan with his eyes open and to stay as still as possible while the MRI scan was performed. The same procedure was used to acquire MRI data from the control participants.

Neuropsychological testing

The following neuropsychological tests were included and are briefly described here.

- *The National Adult Reading Test* (NART—Nelson, 1982) to measure premorbid intelligence.
- *The Mini Mental State Examination* (MMSE—Folstein, Folstein, & McHugh, 1975) to measure whether the patient was oriented for person, place, and time.
- *The Rey Auditory Verbal Learning Test* (Schmidt, 1996) to measure verbal memory encoding and retroactive and proactive aspects of memory interference. In this test, participants are required to recall a list of fifteen unrelated words over five trials (A1 to A5), before being given a different list of fifteen words to recall for one trial only (B1), followed by a sixth trial of the original list (A6), and a seventh trial (A7) after 20 minutes without a review of the first list.

- *The Letter Fluency Test* (letter F, A & S each time at 60 seconds—Thurstone, 1938) to measure the efficiency of retrieval strategies and semantic memory organization.
- *Digit Span* (Wechsler Memory Scale, WMS-III, 1997) to assess auditory verbal working memory capacity.
- *Sustained Attention to Response Task* (SART—O’Connell et al., 2009; Robertson, Manly, Andrade, Baddeley, & Yiend, 1997) to measure response inhibition to infrequent target stimuli presented randomly during a continuous performance go/no-go task.
- The *Test of Everyday Attention* (TEA—Robertson, Ward, Ridgeway, & Nimmo-Smith, 1994) was also carried out during a second session. This battery provides norm-referenced scores on eight different subtests that are sensitive to selective attention, sustained attention, and attentional switching. There is also a divided attention test in the battery. Subtests that load on the selective attention factor are the “Map Search” and the “Telephone Search”. The “Elevator Counting”, the “Lottery”, and the “Telephone Search While Counting” are subtests that load on the sustained attention factor. The “Telephone Search While Counting” gives a measure of divided attention. The “Visual Elevator” loads on the attentional switching factor. Subtests that load on the auditory-verbal working memory are: the “Elevator Counting with Distraction”, which has been designed as a test of auditory selective attention and the “Elevator Counting with Reversal”.

Auditory three-stimulus oddball task and event related potentials

A group of 15 age-matched healthy participants completed an EEG assessment in order to compare findings to the patient. Of these, 14 (male = 8; female = 6; mean age = 19.6 years, SD = 1.24 years; mean years of education = 16.7 years; mean IQ = 109) were included in the final analysis of ERP data.

EEG recordings were taken from the patient during a *three-stimulus auditory oddball task*. In this task, the patient was instructed to detect rare target tones (1000 Hz) pseudo randomly presented through headphones among series of frequent non-target tones (900 Hz) and to signal the recognition of the target tone by pressing the left key of the

mouse as quickly and accurately as possible. A brief practice series was presented to allow the patient to become familiar with the task. Four blocks of the three-stimulus auditory oddball task were administered, each of which lasted 7 minutes. Each 7-minute block consisted of 656 standard stimuli at 900 Hz tone, 83 target stimuli at 1000 Hz and 81 distractor stimuli that were composed of white noise bursts. Each stimulus was 60 ms long with an ITI of 2075 ms. The same procedure was used to test healthy participants and record their EEG activity.

Continuous EEG was acquired through the ActiveTwo Biosemi electrode system from 64 scalp electrodes, digitalized at 512 Hz. Vertical eye movements were recorded with two electrodes, one above and another one below the left eye, while horizontal eye movements were measured with two electrodes at the outer canthus of each eye recorder horizontal movements. Data were analyzed using Besa Version 5.2 (Brain Electric Source Analysis) software (<http://www.besa.de>). Data were re-referenced offline to the mastoid channels and low-pass 0-phase shift dB 40 Hz filter. Stimulus locked data were segmented into epochs of 100 ms before to 650 ms after stimulus onset and baseline corrected relative to the interval from -100 to 0 ms. ERP component structure was confirmed by visual inspection of grand-average waveforms. The width of the latency window used to measure component amplitude was based on the duration and spatial extent of each component. The early component N1 was analyzed in distractor, standard, and target waveform. Subject-specific maximal scalp locations were selected for each individual. The early component N1 was strongest at electrode Cz. The early component N1 was measured as the peak negativity was between 90 and 150 ms. P3a component was analyzed for distractor and standard stimuli. P3a was strongest at electrode Cz and it was measured as the peak positivity between 150 and 300 ms. Finally, P3b component was analyzed on target and standard stimuli. P3b was strongest at electrode Pz and it was defined as the later peak positivity between 250 and 450 ms. A one-sample *t*-test was carried out to assess if the patient’s ERP values were significantly different from control data.

Voxel-based morphometry (VBM)

A separate all-male, right-handed control group ($n = 16$; mean age = 28.6 years, SD = 7 years) with

no known history of neurological or psychiatric disorders was recruited for VBM analysis.

A high-resolution T1-weighted anatomic MPRAGE image (FOV = 230 mm, thickness = 0.9 mm, voxel size = 0.9 mm × 0.9 mm × 0.9 mm) was acquired from the patient and compared to the control group. All MRI data were collected on a Philips 3T Achieva MRI Scanner (Trinity College Dublin). T1-weighted images were processed in SPM8 (www.fil.ion.ucl.ac.uk/spm) using the default settings of the VBM8 toolbox (r435). Modulated gray and white matter images were smoothed with an 8-mm (FWHM) gaussian kernel. Based on other VBM case studies (Muhlau et al., 2009), we used a two-sample *t*-test with variance set to equal, to compare the patient with the control group. Images were masked using an absolute threshold of 0.1. Results were corrected for multiple comparisons (FWE corrected, $p < .05$).

RESULTS

Subjective measures of everyday life deficits

At the first assessment interview, the patient reported problems with attention and memory. Primarily he described difficulties in following conversations with one person in a noisy environment or with several people even if in a quiet place. He complained that background noises or visuo-spatial shifts in background objects distracted him and this led to rapid fatigue, especially during challenging tasks or complex activities.

Neuropsychological testing

The patient's neuropsychological profile is outlined in Table 2. To summarize, the patient's pre-morbid IQ measured by the NART was above average. His working memory capacity, assessed by Digit Span and Elevator Counting with Reversal, was in the normal range. Tests of executive function, in particular, attention switching, measured by the Visual Elevator test and retrieval proficiency from semantic memory, measured by the Letter Fluency test were both intact. When sustained attention was measured under simple monotonous conditions, with a unitary target to detect in Elevator counting subtest and the Lottery subtest of the TEA, standardized scores were in the possibly abnormal range and normal range, respectively.

TABLE 2
Patient's performance on neuropsychological examination

Test	Patient's score	Normal score
<i>Premorbid I.Q.:</i>		
NART ^a	108	100
<i>Auditory Verbal Working Memory:</i>		
Backward Digit Span ^b	14	10 (3)
Elevator Counting with Reversal ^c	7	> = 4
Elevator Counting with Distraction (auditory selective attention) ^c	3*	> = 4
<i>Executive control:</i>		
Visual Elevator (attention switching) ^c	4.19	< = 4.6
Letter fluency (FAS) (retrieval proficiency) ^d	32	40.5 (10.7)
<i>Sustained attention & response inhibition:</i>		
Random SART ^e :		
• Commission errors	7*	3.08
• Omission errors	3*	0.69
• Response time (ms)	138.6*	451.04
• Standard deviation	160.19	85.96
• Coefficient of variation	1.16*	7
Elevator Counting ^c	6**	7
Lottery ^c	10	> = 8
Telephone Search While Counting ^c	3.01*	< = 2.5
<i>Memory:</i>		
The Rey Auditory Verbal Learning Test ^f		
A5 (short memory)	10*	14 (1)
A6 (short memory/interference)	6*	11.30 (0.89)
A7 (retrieval)	7*	10.90 (2.91)
Proactive Interference (PI)	1	
Retroactive Interference (RI)	0.60*	
Forgetting Speed (FS)	1.17	
<i>Selective attention:</i>		
Map Search ^c	18*	> = 32
Telephone Search ^c	3.49*	< = 3.4

*Impaired performance. **Possibly abnormal. ^aNelson (1982).

^bWSM-III (1997). ^cFor norm-referenced scores: Robertson et al. (1994). For controls' reference scores: McAvinue et al. (2012).

^dThurstone (1938). ^eRobertson et al. (1997). ^fSchmidt (1996).

The patient showed clear impairments under conditions of selective attention in the context of distraction in both the visual domain (measured by the Telephone Search While Counting subtest and the Map Search subtest of the TEA) and the auditory domain (measured by the elevator counting with distraction). The patient also showed a response inhibition deficit, producing significantly more false presses on a go/no-go task (random SART) compared to a control sample. A more detailed analysis of random SART key variables was conducted with one-sample *t*-tests to

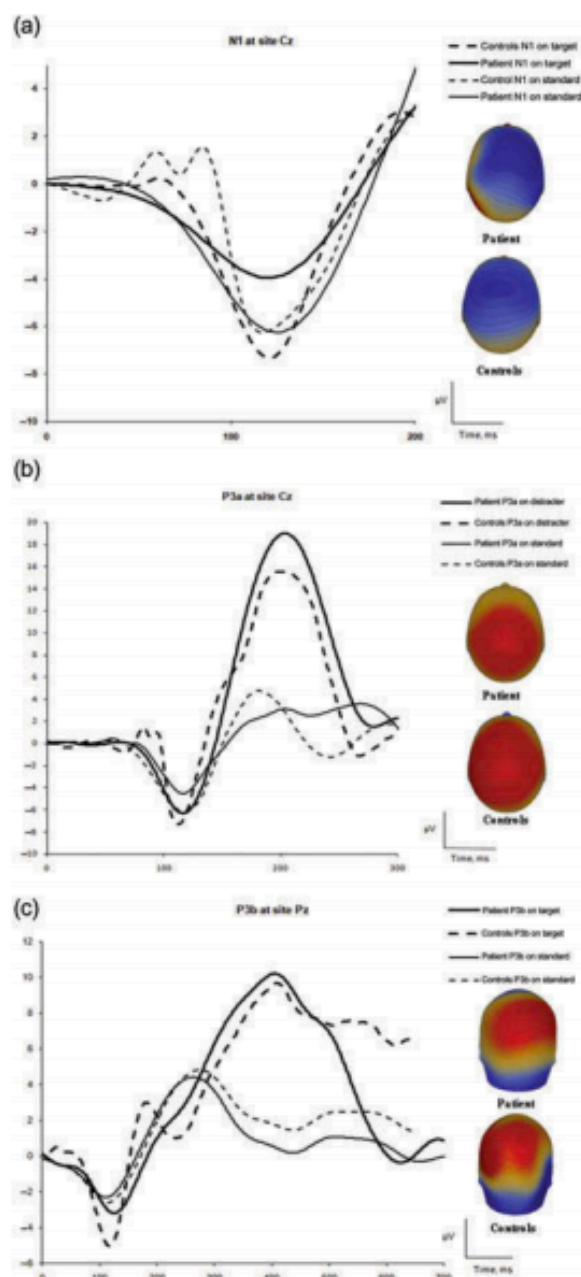


Figure 1. (a) On the left, the patient and controls' grand average N1 waveforms at the Cz recording site for target stimuli. Standard tones waveforms are also displayed in the graph. On the right, N1 topography. (b) Grand average P3a at the Cz recording site for distractor stimuli for controls and the patient. Standard waveforms are also displayed (left). On the right, P3a topography. (c) The patient and controls' grand average P3b at the Pz recording site for target stimuli (left). Standard stimuli waveforms are also displayed. On the right, P3b topography. [To view this figure in color, please see the online version of this Journal.]

DISCUSSION

We report a unique patient who experienced an autoimmune coma, with progressive unresponsiveness continuing over 4 years. The patient went

from a state of unresponsiveness with eyes closed, twitching due to myoclonus, and required spoon-feeding at home by his parents and nasogastric feeding in hospital all of which dramatically improved over months with immunosuppression and post-thymectomy. Nonetheless, a spectrum of cognitive abnormalities emerged, despite the positive response to immunosuppression and these are examined here.

At interview, the patient reported everyday life difficulties in selective attention, particularly problems in filtering out irrelevant information, and problems with episodic memory. The patient's scores on questionnaires confirmed a high frequency of subjective attention and memory complaints in activities of daily living. It is noteworthy that the patient did not experience a general decline across all cognitive measures, as might be expected if fatigue and hypoarousal were the exclusive repercussions of the autoimmune condition. Instead, cognitive impairment was selective and there was sparing of function in several domains.

Although it is not possible to definitively separate the influence of coma length and disease-related encephalopathy in this case, three lines of evidence suggest that pathology, as opposed to the long period of coma, may have given rise to the cognitive impairment. First, the reduced white matter volume in the medulla compared to healthy controls suggests a potential locus of encephalopathy as opposed to more general brainstem atrophy that might be associated with a prolonged coma. Second, the neuropsychological profile of the patient showed specific impairments in selective aspects of cognition, consistent with his reported symptoms and the theoretical framework of brainstem–thalamic interactions that mediate gating of sensory transmission. Third, the ERP findings showed both a reduced amplitude component, reflecting poor selective attention and an increased amplitude component associated with impaired gating of irrelevant stimuli. This pattern of neural response is consistent with an impaired gating mechanism and is not consistent with general or “non-specific” degradation of brainstem functioning.

With respect to neuropsychological function, the patient's performance on three subtests of selective attention from the TEA were below the normal range, indicating that the patient's syndrome has affected his ability to focus attention on one source of information to the exclusion of others. Another subtest of the TEA that measures divided attention

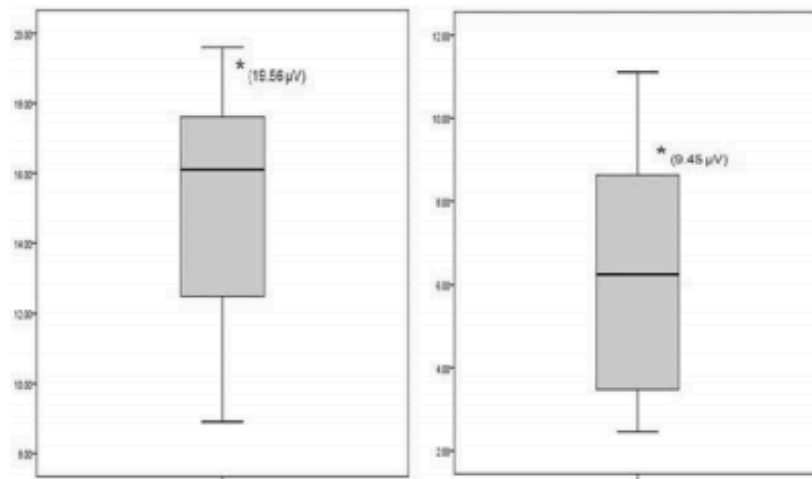


Figure 2. Box plots for P3a peak amplitude (left) and P3b amplitude (right). *Patient's ERP value.

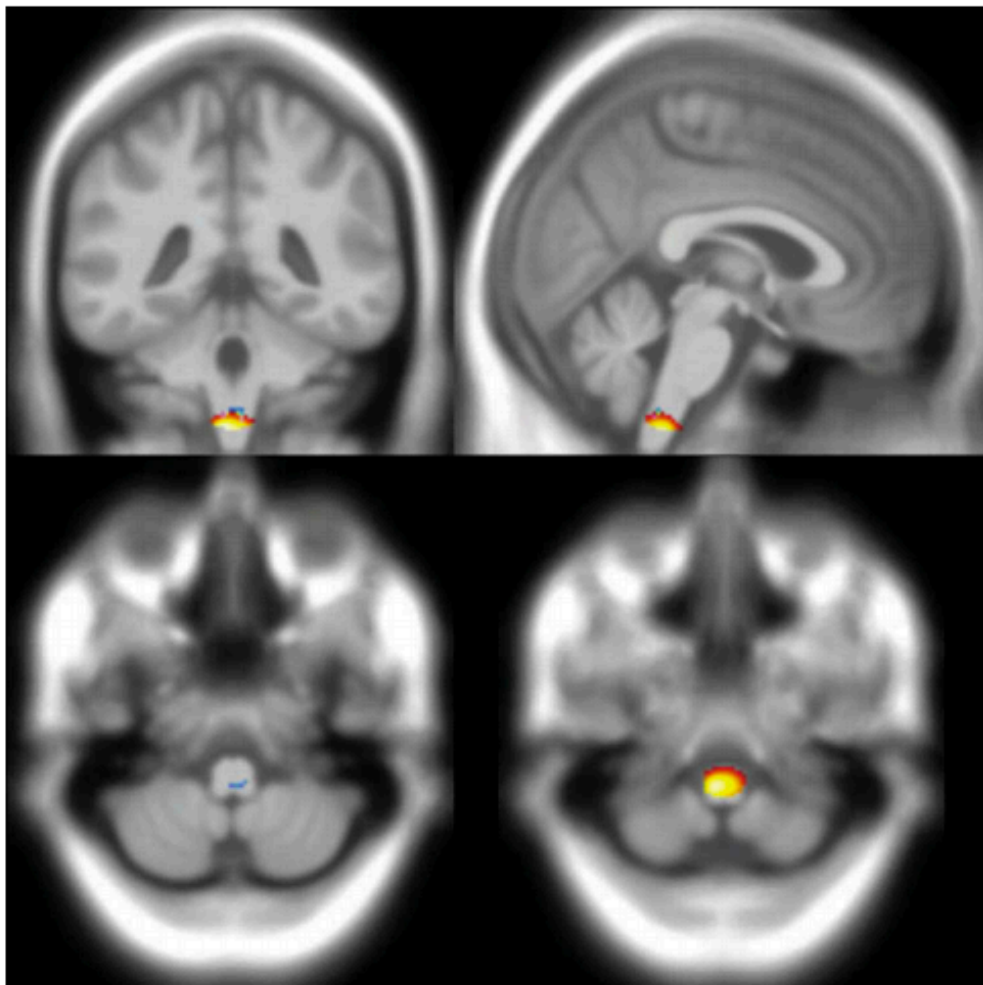


Figure 3. VBM analysis showing significant decrease in WM in the patient compared to controls (red-yellow cluster). Results are displayed at FWE $p < .05$. [To view this figure in color, please see the online version of this Journal.]

was also impaired, suggesting a deficit in redistributing selective attention between two or more sources or types of information.

Selective attention impairment was further evident from electrophysiological analysis of the auditory three-stimulus oddball task. The patient showed an attenuation of the N1 component on target trials relative to the control group, suggesting inefficient early selection of target information. Nevertheless, the subsequent P3b evoked on target trials was marginally greater in amplitude for the patient than the controls suggesting a greater allocation of neural resources to target processing. A larger P3b may be indicative of greater cognitive effort, perhaps compensating for the early filtering deficit by increasing the response to target stimuli at a later stage of attentional elaboration. A robust P3b in the patient is also consistent with the absence of target errors in the auditory oddball task. However, on distractor trials during the oddball task, the P3a component was significantly enhanced in the patient compared to control participants. An enhanced P3a elicited by bursts of white noise may indicate hypersensitivity to task-irrelevant stimuli, which may reflect a neurophysiological marker of increased distractibility. Alternatively, an enhanced P3a may reflect inappropriate deployment of attention to non-target information. Enhanced P3a to novel and distracting stimuli have been demonstrated in adults with closed head injury (Kaipio et al., 1999) and ADHD children in response to novel sounds (Gumenyuk et al., 2005). Both of these clinical groups also report behavioral problems of distractibility.

A second important finding emerges from the patient's subjective memory complaints recorded by the CFQ and EMFQ. The main aspect of his memory impairments appears to be in acquiring new information such as people's names and new phone numbers. The patient's immediate and delayed memory was evaluated in the RAVLT and they were both impaired. It is likely that the patient's memory deficits may be explained, in part, by poor selective deployment of attention during memory encoding. Interference measures of proactive interference and retroactive interference were examined. The patient's proactive interference score was within the normal range; however, his retroactive interference score was impaired. This suggests that learning new material (in this case, a second distracting list presented after five repetitions of a first target list) had detrimental effects on the recall of previously learned material; therefore the

introduction of a distracting element significantly reduced the ability to recall previously learned information. Decreased recall performance in the context of new and distracting information suggests that memory representations of older information are rendered inaccessible. Finally, speed of forgetting was not impaired in this patient, but his below average score suggested that repetition of the learning material did not lead to complete transfer and consolidation of material to long-term memory.

A third significant finding is that, although the patient's syndrome has affected selective cognitive functions, other cognitive functions appear to be spared. Working memory and auditory-verbal working memory are intact as measured, respectively, by the Digit Span and the Elevator Counting with Reversal. Attentional switching measured by the Visual Elevator task was also intact, indicating good mental flexibility. Sustained attention was measured by two subtests of the TEA and the random SART. The subtests of the TEA indicate that patient's ability to detect targets during continuous performance is overall within the normal range. However, the patient committed more false presses to target stimuli and showed greater intra-individual variability than control subjects on the random SART. In this test, presenting the stimuli in random order places greater emphasis on response inhibition. Increased errors on this task reflect impaired inhibitory control in the context of an infrequent no-go trial. In summary, the patient had less problems detecting and responding to targets when attention was challenged over time; however, when the response contingency was reversed requiring the patient to withhold, instead of respond to targets, inhibitory errors resulted.

The pattern of neuropsychological findings in this patient is interesting in the context of other isolated subcortical lesion patients described in the literature (Garrard et al., 2002; Hoffmann & Schmitt, 2004). There is agreement that brainstem lesions in the absence of cerebral insult are commonly associated with cognitive impairment. However, there is no clear evidence that different patterns of cognitive impairment relate in a systematic way to particular lesion sites in the brainstem. Nevertheless, attention and executive function deficits have been more frequently reported than memory, perceptual, and general intellectual function impairments. The detailed analysis of the current patient with neuropsychological assessment, VBM, and ERPs allows a tentative interpretation

of the role of lower brainstem regions—specifically the medulla—and its role in modulating cognitive function.

With respect to the patient's underlying neuropathology, it was hypothesized that an autoantibody/paraneoplastic antibody originating from the patient's thymic hyperplasia had affected part of the reticular activating system. Clinical examinations have been conducted to identify the specific antibody that may have caused the autoimmune coma. So far, paraneoplastic antibodies (anti-Hu, anti-Ri, anti-Yo, anti-Ma), voltage-gated potassium channel (VGKC) antibodies, anti-neuronal antibodies, thyroid autoantibodies, *N*-methyl-d-aspartate (NMDA) receptor antibodies, and anti-glycine antibodies have been investigated, but outcomes have been negative and further examinations are ongoing. However, the results of VBM analysis revealed a significant decrease in white matter in the patient's medulla compared to a group of healthy age-matched controls. Evidence suggests that dorsomedial regions of the medulla provide a direct inhibitory synaptic input to the locus coeruleus–noradrenergic system (Ennis & Aston-Jones, 1989a, 1989b). It is possible that if this inhibitory pathway is compromised due to medulla damage, a more maladaptive pattern of LC tonic discharge will result. Aston-Jones and Cohen (2005b) have argued that poorer attentional focus and distractibility are linked to higher levels of tonic LC activity. An additional behavioral marker that may also be indicative of tonic LC activity is variability of performance. Evidence suggests that RT distributions are wider when the discrimination between targets and distractors are poorer (Aston-Jones & Cohen, 2005a). In this regard, it is noteworthy that the patient showed heightened response time variability compared to controls during the oddball task and the random SART.

Alternatively, it is possible that damage to the caudal medulla may disrupt noradrenergic innervations to midbrain dopamine neuronal regions. Recent anatomic evidence shows that there are medullary noradrenergic afferents pathways to dopamine areas in the midbrain, and these noradrenergic innervations provide visceral-related inputs to reward-related dopamine regions (Mejias-Aponte, Drouin, & Aston-Jones, 2009). If reward-related signals in dopamine areas are dampened due to reduced medullary noradrenergic input, we speculate that the patient's poorer attentional focus may

be explained by reduced dopamine transmission between midbrain and reticular thalamic pathways.

CONCLUSIONS

We report a rare case of a patient with significant white matter reduction in the medulla who exhibited specific impairments of selective attention and memory. Human-evoked potentials revealed reduced NI amplitude response to target information and enhanced P3a responses to task-irrelevant stimuli—corroborating the neuropsychological evidence and pointing to impairments in attention selectivity and susceptibility to interference. These selective cognitive impairments in a case of immunologic brainstem encephalopathy provide a unique view of the impact of subcortical damage on selective attention and memory.

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