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ORIGINAL COMMUNICATION

Cognitive function in the locked-in syndrome

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Abstract *Objective* The locked-in syndrome (LIS) originates from a ventro-pontine lesion resulting in a complete quadraplegia and anarthria. Classically, communication remains possible by means of spared vertical eye movements and/or blinking. To allow assessing cognitive functions in LIS patients, we propose here a neuropsychological testing based on eye-coded communication. *Methods* Ten chronic LIS survivors were assessed 1 to 6 years after their brain insult. One patient was evaluated subacutely (at 2 months) and retested at 6 and 16 months. Neuropsychological testing encompassed short- and long-term memory, attention, executive functioning, phonological and semantic processing and verbal intelligence. *Results* None of the patients showed alterations in verbal intelligence. Impairments in one or several tests were found in five patients. In three of these patients, neuropsychological deficits could be related to additional cortical or thalamic structural brain lesions. In the other 2 patients, weakness or signs of fatigue only were observed in one or two cognitive tasks. Repeated measures in a subacute patient with pure brainstem lesion indicate the recovery of good levels of cognition 6 months after injury. *Conclusion* Results indicate that LIS patients can recover intact cognitive levels in cases of pure brainstem lesions, and that additional brain injuries are most likely responsible for associated cognitive deficits in the LIS. Furthermore, a systematic neuropsychological assessment in LIS patients would allow detecting their cognitive deficits, which will contribute to improve their quality of life and of communication with family and medical caretakers.

Key words cognition · locked-in syndrome · tetraplegia · brain injury · brainstem · thrombosis

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Introduction

The locked-in syndrome (LIS) is characterized by a motor de-efferentation producing paralysis of all four limbs and anarthria, most often resulting from a brainstem lesion. In about 60 % of cases, LIS is caused by a basilar artery occlusion or pontine hemorrhage, but it can also be caused by traumatic brain injury [28]. The classical LIS patient cannot move any part of his or her body (even if sensations are spared) except for vertical eye movements and/or blinking which permit communication [30]. Two variants are (a) the incomplete LIS where the patient has recovered remnants of voluntary motion and (b) the total LIS where there is a complete immobility including even eye movements [3]. In classical and incomplete LIS, an elementary code of communication can be established early after the acute brain insult by means of preserved voluntary eye movements (e. g., looking up for 'yes' or closing the eyes for 'no'). Cognitive function of these patients is supposed to be spared because of the localization of the brain lesion, in principle limited to the ventral pons. However, a PET study by Levy et al. reported a 25 % reduction in cerebral metabolism in LIS patients as compared to healthy controls [23]. On the other hand, a survey conducted by the French Association for LIS (ALIS; http://alis-asso.fr) in 44 patients showed that six patients (14 %) self-reported experiencing attentional problems and eight (19 %) reported having memory problems [22]. Still, an extensive evaluation of cognitive functioning (including the assessment of short- and long-term memory and attention) in a cohort of LIS survivors remained to be conducted. This task is made very difficult due to the impossibility to use standard verbal or motor response modalities.

In this report, we propose a comprehensive battery of standardized neuropsychological tests adapted to a response mode limited to simple eye movements, a technique that can be employed at the LIS patient's bedside. This battery aimed at testing the major cognitive functions including short- and long-term memory, attention, executive function, language and verbal intelligence. It was administered to 10 chronic LIS survivors, 1 to 6 years after their acute brain insult. In one patient, assessment was made subacutely (2 months after admission) and then again at 6 and 16 months. We aim here at providing a useful and validated bedside tool to assess cognitive functioning in LIS without external aids of communication, hence operational in the acute setting.

Methods

Patients

Ten chronic LIS survivors (age range: 24–57 years; 4 females) participated in this study. In all patients, LIS resulted from an ischemic brainstem lesion except for patient 10 who suffered a traumatic brain injury and patient 6 who had a mixed traumatic/hypoxic brain insult (see Table 1). Nine patients were assessed on a single occasion on average 4 years post-injury (range 1–6 years) and one patient (patient 1) was assessed at 2, 6 and 16 months post-injury. All patients presented spontaneous breathing, bilateral spastic quadriparalysis, bilateral Babinski's sign and aphonia. The patients had sustained eyes opening and movements (i. e. vertical consistent tracking and fixation) with response to visual threat. Clinical and structural imaging data are shown Table 1.

Healthy controls

For the tasks that needed structural adaptation to the ocular response mode used in this study, control data were obtained in a group of 40 healthy adults (i. e., forward digit span, backward digit span, auditory sustained attention task and Wisconsin Card Sorting Test; see below). Healthy volunteers were matched according to the age and the level of education (see Table 1) and had no significant neurological or psychiatric history. In order to equate the response mode between LIS patients and controls, control participants had to imagine being in a LIS. They were instructed not to move nor speak but to perform the testing exclusively using the ocular response mode used by the LIS patients. For the other neuropsychological tasks requiring no special change in task design or procedure, published standardized normative data were used.

The study was approved by the Ethics Committee of the University of Liège. Healthy controls gave written informed consent and LIS patients' eye-coded informed consent was videotaped. In addition, written informed consent was obtained from each patient's family.

Neuropsychological testing

Short-term memory

Short-term memory was assessed using an adaptation of the standard forward and backward digit span task [38] to a yes-no recognition response mode. This test assesses the capacity to maintain (forward digit span) and manipulate (backward digit span) verbal information in memory during a short period of time. For the forward digit span, sequences ranging from 5 to 9 digits were orally presented by the experimenter to the subject, at a rate of 1 item per second. After the target sequence, a recognition sequence was presented including the same items in identical order or in a different order resulting from the reversal of two adjacent item positions. The participant had to recognize whether the two sequences were the same or different. There were 8 trials for each sequence length. The procedure for backward digit span was exactly the same, except that the participant had to recognize whether the second sequence was exactly the reverse of the first sequence. For backward digit span, there were six trials per sequence length ranging from 3 to 8 digits. For both forward and backward digit span, testing was stopped when response accuracy decreased to 50 % or less for trials on two consecutive sequence lengths. The longest sequence length at which response accuracy was higher than 50 % represented the short-term memory span.

Long-term memory

We used the Doors test in order to assess non-verbal episodic memory, a recognition memory test from the "Doors and People" test battery [2]. Episodic long-term memory defines the capacity to retain and retrieve information and its spatio-temporal presentation context over a long period of time. The Doors test consists in learning two lists of twelve photographs depicting different doors (lists A and B). The learning phase for each list is followed by a recognition phase where 12 sheets are presented, containing one previously presented picture and three distractor pictures. The distractor pictures for the

Table 1 Clinical and structural imaging data of LIS patients

Patients	1	2	3	4	5
Sex (age, years)	female (21)	female (24)	female (49)	male (36)	male (57)
Level of education	2	2	2	3	3
Cause of LIS	basilar thrombosis	basilar thrombosis	basilar thrombosis	basilar thrombosis	basilar thrombosis
Time since acute brain insult prior to testing (years)	0.2, 0.5 and 1.3	6.4	3.4	6.7	1.4
GCS on admission (score on 15)	8	6	3	4	8
Primary mode of communication	Yes: look up No: look down	Yes: one blink No: two blinks	Yes-No with small head movements	Yes: eyes open No: eyes shut	Yes: look up No: look down
Tracheostomy	removed	removed	present	removed	removed
Gastrostomy/jejunostomy	present	removed	present	present	present
MRI examination (T2 contrast)	ventral pons/left cerebellum	centro-pontine, (cerebellar atrophy)	pons/left cerebellum	pons/mesencephalic/ left thalamus (cerebellar atrophy)	pons/left cerebellar peduncle

Table 1 *(continued)*

Patients	6	7	8	9	10
Sex (age, years)	male (57)	male(57)	female (42)	male (47)	male (51)
Level of education	3	3	3	3	3
Cause of LIS	traumatic basilar dissection	basilar thrombosis	basilar thrombosis	basilar thrombosis	trauma
Time since acute brain insult prior to testing (years)	3.4	5	2.6	6.9	1.5
GCS on admission (score on 15)	3	6	8	8	5
Primary mode of communication	Yes: look up No: look down	Yes-No with small head movements	Yes: look down No: look up	Yes: one blink No: look up	Yes: look down No: look up
Tracheostomy	removed	removed	present	removed	present
Gastrostomy/jejunostomy	removed	present	present	present	present
MRI examination (T2 contrast)	pons (central/left)/ bilateral cerebellar	pontine/ diffuse peri-ventricular	pons/cerebellar (bilateral)/thalamic	pons/mesencephalic	left temporal extradural hematoma/diffuse bifrontal/ left parietal/left thalamus

Note: Level of education 2 represents formal education until age 18 and level 3 represents formal education after age 18

second list are more difficult to reject as they are more closely matched to the target picture. The maximum possible score is 24. For this study, the examiner pointed out each picture of the recognition sheets during several seconds. Using his/her own communication code, the LIS patient only reacted when he/she recognized the picture that was being pointed to as one of the pictures shown during the learning phase. We calculated the number of correct recognitions for list A and list B separately, and the total score summing correct recognitions over parts A and B.

Attention

An auditory attention task was specifically designed for the purpose of this study, based on the sustained attention task from the computerized attention test battery developed by Zimmermann and Fimm [39]. Sustained attention is the capacity to maintain focused attention during a relatively long period of time. Using an audio-CD, we presented a continuous sequence containing low-frequency (450Hz), medium-frequency (1000Hz) or high-frequency (2000Hz) sine wave tones appearing at regular intervals (inter-stimulus interval 1 s). Each sound had a duration of 250 ms and the task had a total duration of 8 min 20 s. The subject had to respond via pre-arranged eye-movements each time he/she detected two consecutive sounds that were identical (low-low, medium-medium or high-high). The score represented the number of items correctly detected.

Executive functioning

Executive functions were assessed by measuring the capacity to develop and adapt cognitive strategies to a new situation where automated reactions are not valid anymore. This was done by administering the Wisconsin Card Sorting Test (WCST) measuring planning, categorization, strategy change and inhibition abilities [4]. A shortened version was used here in order to prevent fatigue effects due to the eye-movement response mode. According to the standard procedure of the WCST, a set of cards (here, 64 cards) as well as four target cards were placed before the subject on a board. Each of these cards had several characteristics as determined by the color, the shape or the number of the printed symbols. The participant had to guess which of these dimensions would be used to match the first card of the set with one of the four target cards. The examiner showed each of the four cards and the participant answered with an eye sign for "yes" when the examiner showed the card where the participant wanted to place the first card of the set. A feedback was given for each response and, after 10 consecutive correct responses, the examiner changed the classification criterion without informing the subject. In the present study, the task was stopped when the patient had correctly sorted the cards along each of the three dimensions. The score was represented as the percentage of erroneous responses relative to the total number of responses.

Language

Phonological and semantic language processing was assessed using an oral word–picture matching task (LEXIS) [11]. For each spoken word, five pictures were presented, including the target picture as well as neutral, phonologically related or semantically related distractor pictures. The patient had to respond by pre-arranged eye movements only when the picture being pointed to match the word pronounced by the examiner. The score was expressed as the number of correct responses over a total of 80 target items.

Verbal intelligence

The French adaptation of the Peabody Picture Vocabulary Test ("Echelle de Vocabulaire en Images Peabody" ou EVIP) was used to estimate verbal intelligence [14]. The test consists of 170 nouns, verbs or adjectives spoken by the examiner, organized as a function of level of difficulty. For each item, four pictures are presented, one being the target and the others being distractors. The subject has to determine which one of the four pictures corresponds to the target word. As we exclusively assessed adult patients in this study, we started at the item 120. Testing was stopped according to published stop criterion (i. e., after 6 erroneous responses for 8 consecutive trials). The patient had to respond by eye movements when the picture being pointed to by the examiner provided the best match with the pronounced target word. The raw score (i. e., the number of the last item performed minus the number of incorrect responses) was converted to a normalized score based on a previously published French-speaking normative reference group [14].

General procedure

Each patient was assessed at the bedside in hospital (n = 9) or at home (n = 1). Each patient used his/her personal communication code for yes/no responses, as summarized in Table 1. Note that patients 3 and 7 had partially recovered from their LIS given that they communicated using small head movements at the time of testing. In order to increase the reliability of responses, patients and healthy controls had to respond twice for each test item. The testing was performed in the following order: forward digit span, backward digit span, Doors test, auditory sustained attention task, LEXIS, WCST and EVIP. Each task was preceded by a series of practice items in order to ensure correct understanding of the task.

Statistical analysis

In order to reflect as much as possible standard clinical neuropsychological assessment procedures, results were analyzed at the individual level by determining whether each patient's performance level for a given task was outside the control population range using either performances 2 standard deviations below control mean (forward and backward digit span, auditory sustained attention task, WCST and LEXIS) or performances below percentile 2.5 relative to the control population (Doors test; EVIP). For the criterion of 2 standard deviations below performance of the collected control data, the significance was further checked by performing modified t-tests, as recently proposed by Crawford and Garthwaite [9] in order to determine whether an individual patient's score is significantly different from control performance ($p < 0.05$). The t-test was not performed for the other tasks (Doors test and EVIP) which use percentile as normative value.

Results

Table 2 shows neuropsychological results in the LIS patients and the corresponding normative reference values. Four patients (patients 1, 2, 3 and 9) were within normal range for all tasks. As compared to the 40 matched healthy controls, patients 4, 6, 7 and 10 showed impaired storage in short-term memory as evaluated by the forward digit span task. Patients 4 and 10 also showed impaired performance for the backward digit span (evaluating the capacity to store and to manipulate information in short-term memory). Patients 4 and 8 showed subnormal results (i. e., just below the threshold) on the Doors test (evaluating long-term memory). Patient 8 showed impairments in the auditory sustained attention task. Patients 4, 5 and 10 showed subnormal performance on language function as measured by the LEXIS. Note however that patients 4 and 5 committed all errors in the last part of the test. The LEXIS could not be finished in patient 6 due to fatigue. Patients 7 and 10 showed impairment on the WCST assessing executive functioning. No impairment was observed for vocabulary knowledge and verbal intelligence, as measured by the EVIP test.

In patient 1, tested on 3 separate occasions (2 months, 6 months and 1.3 years after her brainstem infarction), attentional dysfunction (auditory sustained attention task) was evidenced but resumed at 6 months. It should be noted that the testing at month 2 was divided into four sessions because of the patient's fatigability. At 6 months, patient 1 only showed language related difficulties as scored by the LEXIS (the EVIP was not administered at that time). As mentioned above, at 1.3 years the patient no longer showed significant dysfunction on any task.

Discussion

Our comprehensive neuropsychological testing indicates the absence of extensive cognitive deficits in LIS patients following an acute brainstem lesion. Four LIS patients showed normal cognitive levels in all tested domains, whereas the others exhibited impairment on one or more tests. However, it is likely that a part of these patients' additional supra-tentorial brain damage may explain their observed cognitive deficits. Patients 4 and 8 were suffering from additional thalamic lesions, known to impair recognition memory [15, 19, 40], short-term memory [8] and attention [16, 34]. In patient 10, the dorsolateral prefrontal cortical lesion could account for the observed alteration in executive functioning [17, 31, 37] and short-term memory [24], whereas the temporal lesion might be related to the impaired language comprehension [13]. Likewise, some deficits might be attributable to higher fatigability in LIS patients. Patients 4 and

Table 2 Neuropsychological tests results in LIS patients

Patients	1			2	3	4
Time since brain injury	2 months	6 months	16 months	6.5 years	3.5 years	7 years
Short memory						
Digit span	7 (7 ± 1.2)	6 (7 ± 1.2)	9 (7 ± 1.2)	9 (7 ± 1.2)	8 (7 ± 1.2)	3[b] (8.5 ± 0.8)
Backward span	6 (4.2 ± 0.9)	5 (4.2 ± 0.9)	7 (4.2 ± 0.9)	4 (4.2 ± 0.9)	3 (4.2 ± 0.9)	2[b] (6.9 ± 1.3)
Long-term memory						
Doors test	16 (P10)	20 (P50–75)	17 (P10–25)	22 (P75–90)	16 (P10–25)	12[a] (P1)
Attention						
Auditory sustained attention task	35[b] (39.3 ± 1.6)	40 (39.3 ± 1.6)	39 (39.3 ± 1.6)	37 (39.3 ± 1.6)	39 (39.3 ± 1.6)	39 (39.1 ± 2.0)
Executive function						
Wisconsin Card Sorting Test	10 (21 ± 7)	21 (21 ± 7)	14 (21 ± 7)	30 (21 ± 7)	33 (21 ± 7)	21 (16 ± 8)
Language						
LEXIS	79 (79.1 ± 0.7)	73[b] (79.1 ± 0.7)	79 (79.1 ± 0.7)	78 (79.3 ± 0.9)	78 (79.3 ± 0.8)	76[b] (79.3 ± 0.8)
Verbal intelligence						
EVIP	86 (P15)	NA	86 (P15)	> 128 (P97)	119 (P90)	101 (P50)

Patients	5	6	7	8	9	10
Time since brain injury	1.5 years	3.5 years	5 years	2.5 years	7 years	1.5 years
Short memory						
Digit span	6 (8 ± 1.3)	5[b] (8 ± 1.3)	5[b] (8 ± 1.3)	9 (8 ± 1.3)	8 (8 ± 1.3)	4[b] (8 ± 1.3)
Backward span	8 (5.1 ± 1.7)	4 (5.1 ± 1.7)	5 (5.1 ± 1.7)	8 (5.1 ± 1.7)	8 (5.1 ± 1.7)	2[b] (5.1 ± 1.7)
Long-term memory						
Doors test	14 (P10)	17 (P25)	21 (P75–90)	12[a] (P1)	20 (P50)	19 (P50–75)
Attention						
Auditory sustained attention task	42 (38.2 ± 2.2)	36 (38.2 ± 2.2)	40 (38.2 ± 2.2)	34[b] (38.2 ± 2.2)	41 (38.2 ± 2.2)	42 (38.2 ± 2.2)
Executive function						
Wisconsin Card Sorting Test	2 (16 ± 8)	15 (16 ± 8)	41[b] (16 ± 8)	13 (16 ± 8)	9 (16 ± 8)	42[b] (16 ± 8)
Language						
LEXIS	77[b] (79.3 ± 0.5)	NA	79 (79.3 ± 0.5)	78 (79.3 ± 0.8)	79 (79.3 ± 0.8)	63[b] (79.3 ± 0.5)
Verbal intelligence						
EVIP	120 (P90)	> 128 (P97)	> 128 (P97)	119 (P90)	> 128 (P97)	87 (P19)

[a] performances 2.5 % (P) or less below published normative control data; [b] 2 standard deviations below control means and significant difference at $p < 0.05$ using modified t-test for single-subject analysis [9]
NA not administered

5 produced errors in the LEXIS solely in the last part of the testing, which seemingly reflects exhaustion rather than a true language deficit. In the absence of difficulties on any other task, patient 5 should in our view not be considered as cognitively impaired. Finally, other patients' testing results appeared to reflect a subnormal weakness rather than a factual cognitive deficit. Although impairment in short-term memory was statistically significant in patients 6 and 7 (both showing no documented structural cortical brain lesion), it should be emphasized that their performance (digit span of 5 in both patients) was close to the inferior limit of the normal range (i. e., 5.4 for healthy controls). Similarly, the high percentage of errors made by patient 7 in the WCST was encountered only after the first change of category. In case of genuine perseverative errors (i. e., when the patient cannot inhibit the answer even if he knows this is wrong), patient 7 should have continued to persevere in the third category, which was not observed. On the contrary, the patient showed a 20 % decrease of errors between the second and third category, indicating that he was able to detect categories changes and to maintain the chosen strategy. Hence, it is not likely this patient really presented major executive dysfunction. Finally, we argue that the performances of all these patients (patients 4, 5, 6 and 7) are maybe underestimated due to the cortico bulbar involvement as the presence of uncontrolled motor activity can increase the difficulty to observe volitional and accurate responses.

To sum up, 5 out of 10 LIS survivors studied in the chronic phase (i. e., one year after acute brain injury) showed intact short- and long-term memory, attention, executive functioning, phonological and semantic processing and verbal intelligence. Among patients showing low performances in one or more tasks, 3 showed neuropsychological deficits most likely related to additional thalamic or cortical structural brain lesion (patients 4, 8 and 10). Two other patients with no associated supratentorial brain lesion showed a weakness (maybe due to pseudo bulbar palsy) for some cognitive tasks rather than genuine cognitive deficits (patients 6 and 7). Regarding the longitudinal data obtained in patient 1 (suffering from a pure brainstem lesion), attentional functioning normalized after 6 months, where only language related difficulties persisted. However, the language difficulties presented at this stage could also have been related to the fact that the battery had been presented in a single session. Indeed, for the first assessment, exceptionally divided in several sessions, a good performance had been observed. Therefore, we are inclined to consider that a full resumption of cognition was observed 6 and 16 months post-injury in patient 1.

We observed no significant deficits in LIS without additional supratentorial or mesencephalic lesions. Nevertheless, the ventral pontine lesions causing LIS could have an impact on both the cognitive functions tested and the patient's behavior during the testing. The frontal lobes receive an important afferent input from ascending modulation systems (e.g., mono-aminergic systems). These modulatory neurotransmitter systems are thought to influence cortical plasticity [18] subserving long-term memory [27, 33, 35], executive functioning [10, 20] and attention [10, 26]. In other part, motivation is considered an essential feature defining success rate (and inhibition of errors) in neuropsychological testing. The role of dopaminergic (and probably other ascending aminergic systems) on motivation is well known [12]. In LIS, the lesion usually is located below the mesencephalon and therefore should not have an influence on the ascending dopaminergic system. This may be a reason for the observed absence of cognitive dysfunction, except in patients with supratentorial (patient 10) or mesencephalic (patients 4 and 8) lesions.

Finally, we did not observe a clear relationship between patients' cognitive (dys)function and the presence of cerebellar lesions. Previous studies have also shown that patients with lesioned cerebellum may show normal cognitive functioning [29]. It might be that the frontal cortex (which was intact in our patients showing cerebellar lesions) plays a compensatory role in the cognitive functions (e.g. working memory and executive functioning) previously associated with the cerebellum [7, 24]. Nevertheless, further investigation could be provided to assess more accurately the executive function (i.e. inhibition, planning, shifting, etc.) or the working memory (i.e. central executive) to confirm this result. On the other hand, the role of emotion in the patients' performances could be controlled as dysfunction following cerebellar lesion (particularly, when lesions encroach upon the vermis) is well-known [32].

The observation of intact intellectual abilities in LIS patients without additional supratentorial or mesencephalic lesions is in line with a prior case study [6]. Our results also corroborate two case reports [1, 5] having investigated short- and long-term memory, language and general intelligence in LIS. However, the latter responded to the test using a sophisticated, cognitively demanding computerized communication aid. It is therefore not surprising that these patients showed no cognitive impairment as they were already selected based on their ability to comply with the cognitive requirements of the implemented communication device. Finally, one study [25] longitudinally assessed cognition 6, 12 and 24 months after a basilar thrombosis. Full recovery of performance was observed only after 1 year, but at this time the patient had regained motor and articulatory abilities and actually was no longer in a LIS state.

In conclusion, the presented neuropsychological testing was designed to be both of acceptable completeness and duration to be clinically pertinent and to be operational at the patient's bedside as early as possible after the acute phase of the LIS. Our results illustrate that the new testing battery adapted to eye-coded communication is feasible as early as 2 months after an acute brainstem lesion. However, in our experience, it is not recommendable to administer the complete battery within the first days or weeks after the injury since vigilance and global attention often remain fluctuating and easily exhausted at this stage. Future longitudinal investigations are required to identify the time when full cognitive capacity resumes in LIS survivors recovering from coma caused by a pure brainstem lesion.

The assessment of neuropsychological and cognitive functions is of primary importance for LIS patients whose quality of life is entirely dependent on their arduous communication with the environment. Indeed, it is crucial for LIS survivors to be able to emit their thoughts and feelings unambiguously [21]. Any cognitive deficit that alters the efficiency of the communication processes should be identified as soon as possible. Preserved cognition is also necessary for using the sophisticated patient-computer interfaces developed by experts in rehabilitation engineering and speech-language pathology (e.g. Quick Glance www.eyetechds.com or Eye gaze Communication System www.eyegaze.com/indexdis.htm) permitting LIS patients to communicate more expeditiously and to control their environment (e.g. operate a telephone or fax, or access the world wide web and use e-mail). Erroneous underestimation of cognitive function in LIS survivors may prevent access to such technology and significantly decrease their decision making capacities and quality of life. In this context, this neuropsychological battery could also be validated for other neurological motor diseases such as amyotrophic lateral sclerosis (ALS) where neuropsychological deficits are known [36]. Indeed, in detecting as soon as possible true neuropsychological deficits in patients with motor disease, a tailored rehabilitation program can be provided in order to improve communication between patients and family or caregivers, thus permitting LIS patients to resume a role in society.

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References

1. Allain P, Joseph PA, Isambert JL, Le Gall D, Emile J (1998) Cognitive functions in chronic locked-in syndrome: a report of two cases. Cortex 34:629–634
2. Baddeley AD, Emslie H, Nimmo-Smith I (1994) Doors and people: a test of visual and verbal recall and recognition. Thames Valley Test Company, Flempton, Bury St. Edmunds
3. Bauer G, Gerstenbrand F, Rumpl E (1979) Varieties of the locked-in syndrome. J Neurol 221:77–91
4. Berg EA (1948) A simple objective technique for measuring flexibility in thinking. J Gen Psychol 39:15–22
5. Cappa SF, Pirovano C, Vignolo LA (1985) Chronic 'locked-in' syndrome: psychological study of a case. Eur Neurol 24:107–111
6. Cappa SF, Vignolo LA (1982) Locked-in syndrome for 12 years with preserved intelligence. Ann Neurol 11:545
7. Collette F, Hogge M, Salmon E, Van der Linden M (2006) Exploration of the neural substrates of executive functioning by functional neuroimaging. Neuroscience 139:209–221
8. Constantinidis C, Procyk E (2004) The primate working memory networks. Cogn Affect Behav Neurosci 4:444–465
9. Crawford JR, Garthwaite PH (2002) Investigation of the single case in neuropsychology: confidence limits on the abnormality of test scores and test score differences. Neuropsychologia 40:1196–1208
10. Cropley VL, Fujita M, Innis RB, Nathan PJ (2006) Molecular imaging of the dopaminergic system and its association with human cognitive function. Biol Psychiatry 59:898–907
11. De Partz MP, Bilocq V, De Wilde V, Seron X, Pillon A (2001) LEXIS: Tests pour le diagnostic des troubles lexicaux chez le patient aphasique
12. Dreher JC, Kohn P, Berman KF (2006) Neural coding of distinct statistical properties of reward information in humans. Cereb Cortex 16:561–573
13. Dronkers NF, Wilkins DP, Van Valin RD, Jr., Redfern BB, Jaeger JJ (2004) Lesion analysis of the brain areas involved in language comprehension. Cognition 92:145–177
14. Dunn LM, Thériault-Whalen CM, Dunn LM (1993) Echelles de vocabulaire en images Peabody. Adaptation française du Peabody Picture Vocabulary Test-Revised. Toronto (Ontario)
15. Edelstyn NM, Ellis SJ, Jenkinson P, Sawyer A (2002) Contribution of the left dorsomedial thalamus to recognition memory: a neuropsychological case study. Neurocase 8:442–452
16. Gitelman DR (2003) Attention and its disorders. Br Med Bull 65:21–34
17. Goldstein B, Obrzut JE, John C, Ledakis G, Armstrong CL (2004) The impact of frontal and non-frontal brain tumor lesions on Wisconsin Card Sorting Test performance. Brain Cogn 54(2): 110–116
18. Hummel FC, Cohen LG (2005) Drivers of brain plasticity. Curr Opin Neurol 18:667–674
19. Kishiyama MM, Yonelinas AP, Kroll NE, Lazzara MM, Nolan EC, Jones EG, Jagust WJ (2005) Bilateral thalamic lesions affect recollection- and familiarity-based recognition memory judgments. Cortex 41(6):778–788
20. Kraus MF, Smith GS, Butters M, Donnell AJ, Dixon E, Yilong C, Marion D (2005) Effects of the dopaminergic agent and NMDA receptor antagonist amantadine on cognitive function, cerebral glucose metabolism and D2 receptor availability in chronic traumatic brain injury: A study using positron emission tomography (PET). Brain Injury 19(7):471–479
21. Laureys S, Pellas F, Van Eeckhout P, Ghorbel S, Schnakers C, Perrin F, Berre J, Faymonville ME, Pantke KH, Damas F, Lamy M, Moonen G, Goldman S (2005) The locked-in syndrome: what is it like to be conscious but paralyzed and voiceless? Prog Brain Res 150: 495–511
22. Leon-Carrion J, van Eeckhout P, Dominguez-Morales Mdel R (2002) The locked-in syndrome: a syndrome looking for a therapy. Brain Inj 16: 555–569
23. Levy DE, Sidtis JJ, Rottenberg DA, Jarden JO, Strother SC, Dhawan V, Ginos JZ, Tramo MJ, Evans AC, Plum F (1987) Differences in cerebral blood flow and glucose utilization in vegetative versus locked-in patients. Ann Neurol 22:673–682
24. Muller NG, Knight RT (2006) The functional neuroanatomy of working memory: contributions of human brain lesion studies. Neuroscience 139(1):51–58
25. New PW, Thomas SJ (2005) Cognitive impairments in the locked-in syndrome: A case report. Arch Phys Med Rehabil 86:338–343
26. Nieoullon A (2002) Dopamine and the regulation of cognition and attention. Prog Neurobiol 67:53–83
27. Parton A, Coulthard E, Husain M (2005) Neuropharmacological modulation of cognitive deficits after brain damage. Curr Opin Neurol 18:675–680
28. Patterson JR, Grabois M (1986) Locked-in syndrome: a review of 139 cases. Stroke 17:758–764
29. Piguet O, Bennett HP, Waite LM, Kril JJ, Creasey H, Anthony Broe G, Halliday GM (2006) Preserved cognition and functional independence after a large right posterior cerebral artery infarct: longitudinal clinical and neuropathological findings. Neurocase 12:81–90
30. Plum F, Posner JB (1983) The diagnosis of stupor and coma. Davis, F. A., Philadelphia
31. Romine CB, Reynolds CR (2004) Sequential memory: a developmental perspective on its relation to frontal lobe functioning. Neuropsychol Rev 14:43–64
32. Schmahmann JD, Caplan D (2006) Cognition, emotion and the cerebellum. Brain 129:288–292
33. Schott BH, Seidenbecher CI, Fenker DB, Lauer CJ, Bunzeck N, Bernstein HG, Tischmeyer W, Gundelfinger ED, Heinze HJ, Duzel E (2006) The dopaminergic midbrain participates in human episodic memory formation: evidence from genetic imaging. J Neurosci 26:1407–1417
34. Shipp S (2004) The brain circuitry of attention. Trends Cogn Sci 8:223–230

35. Sterpenich V, D'Argembeau A, Desseilles M, Balteau E, Albouy G, Vandewalle G, Degueldre C, Luxen A, Collette F, Maquet P (2006) The locus ceruleus is involved in the successful retrieval of emotional memories in humans. J Neurosci 26:7416–7423
36. Strong MJ, Grace GM, Orange JB, Leeper HA, Menon RS, Aere C (1999) A prospective study of cognitive impairment in ALS. Neurology 53:1665–1670
37. Stuss DT, Levine B, Alexander MP, Hong J, Palumbo C, Hamer L, Murphy KJ, Izukawa D (2000) Wisconsin Card Sorting Test performance in patients with focal frontal and posterior brain damage: effects of lesion location and test structure on separable cognitive processes. Neuropsychologia 38: 388–402
38. Wechsler D (2001) MEM-III: Echelle clinique de mémoire de Wechsler. Paris
39. Zimmermann P, Fimm B (1994) Tests d'évaluation de l'attention (TEA). Würselen
40. Zoppelt D, Koch B, Schwarz M, Daum I (2003) Involvement of the mediodorsal thalamic nucleus in mediating recollection and familiarity. Neuropsychologia 41:1160–1170