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European neuroborreliosis: neuropsychological findings 30 months post-treatment

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Background: The aim of this study was to compare neuropsychological (NP) functioning in patients with Lyme neuroborreliosis (LNB) 30 months after treatment to matched controls.

Methods: We tested 50 patients with LNB and 50 controls with the trail-making test (TMT), Stroop test, digit symbol test, and California Verbal Learning test (CVLT). A global NP sumscore was calculated to express the number of low scores on 23 NP subtasks.

Results: Mean scores were lower amongst LNB-treated patients than amongst controls on tasks assessing attention/executive functions: (Stroop test 4: 77.6 vs. 67.0, $P = 0.015$), response/processing speed (TMT 5: 23.4 vs. 19.2, $P = 0.004$), visual memory (digit symbol recall: 6.6 vs. 7.2, $P = 0.038$), and verbal memory (CVLT list B: 4.68 vs. 5.50, $P = 0.003$). The proportion of patients and controls with NP sumscores within one SD from the mean in the control group (defined as normal) and between one and two SD (defined as deficit) were similar, but more LNB-treated patients than controls had a sumscore more than two SD from the mean (defined as impairment) (8 vs. 1, $P = 0.014$).

Conclusions: As a group, LNB-treated patients scored lower on four NP subtasks assessing processing speed, visual and verbal memory, and executive/attention functions, as compared to matched controls. The distribution of NP dysfunctions indicates that most LNB-treated patients perform comparable to controls, whilst a small subgroup have a debilitating long-term course with cognitive problems.

Introduction

European Lyme neuroborreliosis (LNB) typically presents as a subacute, painful, and lymphocytic meningoradiculitis (Bannwarth's syndrome) whereas central nervous system involvement with encephalitis or myelitis is rare [1]. The objective manifestations of LNB usually disappear or stabilize after antibiotic treatment, but 10–50% of the patients report persisting complaints such as fatigue, cognitive problems, myalgia, arthralgia, or reduced health-related quality of life (HRQoL) [2–4]. If these complaints persist more than 6 months after antibiotic therapy, the condition is often called post-Lyme disease syndrome [5]. The prevalence of objective cognitive deficits post-LNB is debated [4]. Studies addressing this issue vary substantially regarding methods and patient selection [6–11], and most studies are conducted in the United States (US). In brief, these studies have found different patterns of reduced processing speed, memory, and executive/attention problems amongst patients with post-Lyme syndrome. As both the Borrelia genotype and the clinical picture of Lyme disease in the US differ somewhat from what we find in Europe, the study results are not necessarily transferable to European patients [1].To our knowledge, there is only one controlled European post-LNB study that includes standardized neuropsychological (NP) assessment of cognitive functions [12]. In this study, they found deficits related to memory, mental flexibility, verbal association, and articulation amongst patients with LNB. This study was conducted before standard

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therapy for LNB was established, and not all of the 20 included patients had received antibiotics.

The aim of our study was to compare NP functioning in a group of well-characterized European adult patients with LNB 30 months after treatment to a matched control group.

Methods

Study design

Case–control follow-up.

Patients and controls

From 2004 to 2008, 102 consecutive adult patients from nine hospitals in Norway were included in a LNB treatment study, comparing doxycycline and ceftriaxone [13]. Of practical and geographical reasons, we only included patients from the two hospitals in Agder County, the highest endemic region regarding Borrelia infections in Norway. Clinical score at pre-treatment and 4 months post-treatment as well as the type of treatment did not differ significantly between the patients included in this study and the rest of the patients in the treatment trial (data not shown). Fifty-seven patients were invited by letter to participate 30 months (range 27–34) after treatment, and 50 persons consented and were included. Detailed study design, inclusion, and diagnostic criteria are described elsewhere [3].

Each patient with LNB brought a control person from the same geographical area, matched for age, gender, and education level. Exclusion criterion for the controls was a typical history of LNB. Serological testing of the controls was not carried out as 15–20% of the inhabitants of Agder County are known to have anti-Borrelia antibodies without any history of LNB. Patient characteristics are shown in Table 1.

Table 1 Characteristics of LNB-treated patients and controls (previously published) [3]

Variable	LNB-treated patients (n = 50)	Controls (n = 50)	P-value
Age years, mean (range)	55 (21–76)	56 (20–78)	ns
Gender male n (%)	29 (58)	29 (58)	ns
Married/partner yes n (%)	44 (88)	44 (88)	ns
Secondary education			
0–3 years/4–7 years/≥7 years n	25/15/10	23/13/14	ns
Coexisting diseases n (%)			
Somatic	25 (50)	29 (58)	ns
Previous/present psychiatric	10 (20)	8 (20)	ns
Out of work n (%)			
Total	18 (36)	16 (32)	ns
Because of LNB	5 (10)	0 (0)	ns
Other illness	5 (10)	4 (8)	ns
Old-age	6 (12)	11 (22)	ns
Student/unemployed	1 (2)/1 (2)	0 (0)/1 (2)	ns
Reported subjective complaints n (%)			
Malaise	11 (22)	0 (0)	<0.001
Fatigue	25 (50)	8 (16)	0.001
Pain	16 (32)	21 (42)	ns
Memory problems	23 (46)	5 (10)	<0.001
Concentration problems	17 (34)	4 (8)	0.003
Paraesthesias	17 (34)	7 (14)	0.034

ns, not significant; SD, standard deviation; LNB, Lyme neuroborreliosis.

Clinical variables

The examinations took place at Sørlandet Hospital by one experienced neurologist (RE). All participants were informed that the NP tests assessed different aspects of cognition, like memory and attention, and they were encouraged to perform their best in every test.

A trained neuropsychologist blinded to group adherence scored the NP tests. Clinical and demographic data were collected through a semi-structured interview and clinical neurological examination. Before treatment, 80% of the patients had a complete or partial Bannwart's syndrome, and 8% had symptoms suggesting involvement of the central nervous system (myelitis, ataxia, or confusion). Fifty percent were treated with oral doxycycline and 50% with IV ceftriaxone. Sixty-eight percent were classified as definite LNB and 32% as possible LNB [14]. The scores of the HRQoL questionnaire Short-Form 36 (SF-36), fatigue severity scale (FSS), and Montgomery and Åsberg Depression Rating Scale (MADRS) are previously published; Physical Component Summary (PCS) of SF-36 was 44, Mental Component Summary (MCS) 49, FSS 3.5, and MADRS 3.1 [3]. Three patients had anti-TBE IgG antibodies in serum, and none had anti-TBE IgM antibodies. We did not test for Anaplasma, but none of the patients had a clinical picture or blood count suggestive of Anaplasma infection. The selection of NP tests was based on a review of relevant studies [4,8,10,11,15]. The NP tests were administered in a fixed order, but short breaks were permitted if needed.

Cognitive assessments, neuropsychological (NP) tests

Executive functions and attention

Trail-making test (TMT 1–4) assesses attention and flexibility in solving problems on visual–motor tasks [16]:

TMT 1 (visual scanning): Tick a specific number amongst an array of letters and numbers.

TMT 2: Connect numbers in rising order.
TMT 3: Connect letters in alphabetical order.
TMT 4: (primary executive/attention function): Connect numbers and letters in correct order (i.e., switching between two sets of rules).
Raw scores are the time (s) used to complete the tasks.

The color-word interference tasks 1–4 are an adapted version of the Stroop test [16] that assesses the ability to inhibit a prepotent reaction (impulse control);
Stroop 1: Name colors.
Stroop 2: Read color names.
Stroop 3: Avoid reading the word and instead name the ink color in which the word is written.
Stroop 4: Name the ink color on all words, except those placed within a square, which should be read.
The last two conditions are the primary executive tests and require both the inhibition of reading and the ability to switch between rules.

Raw scores are the time (s) used to complete the tasks.

Processing speed/response speed
The digit symbol test [part of the Wechsler Adult Intelligence scale (WAIS-III)]: Copy symbols paired with numbers during a 120-s interval.

Raw scores are the number of correctly copied symbols [16].
TMT 5: Draw a line between dots as fast as possible.
Raw score is the time (s) used to complete the task.

Memory assessment
Digit symbol cued and free recall test assess visual learning.

Digit symbol cued recall test: Combine symbols and numbers recalled from the digit symbol test.

Digit symbol-free recall test: Write down all symbols recalled from the digit symbol test.

The California Verbal Learning Test (CVLT) assesses verbal learning, short- and long-term memory, and recognition:

CVLT 1–5 (assesses learning by repetition): Remember a word list during five oral presentations.

CVLT list B: Remember a second word list presented once.

CVLT free and cued short recall: Recall the original list after the distracter list in free and cued manner.

CVLT free and cued long recall: After a 20-min brake, recall the original list [17].

The optional trail of the CVLT-II, long delay forced-choice recognition, was included to examine the degree of individual effort: Pick the word from the original list amongst two different words presented immediately after the long delay test [17].

Ethics

All participants gave written informed consent. The study was approved by the Regional Committee for Medical Research Ethics in Southern Norway, and by the Norwegian Data Inspectorate. This trial is a follow-up study on the treatment trial registered with ClinicalTrials.gov number NCT00138801.

Statistical analysis

The statistical software SPSS version 16 (Statistical Package for Social Sciences Inc., Chicago, IL, USA) was used for all analyses. The groups were compared by paired *t*-test and Wilcoxon signed-rank test for paired continuous data, and McNemar test for paired categorical data. Paired test was chosen because of the matched one-to-one cases study design. *P*-values < 0.05 were regarded as significant. The results are reported as mean raw scores with standard deviations (SD) or proportions. To achieve a dimensionless quantity, the scores for each NP subtest were transformed into *Z*-scores. The *Z*-score represents the distance between the patient's raw score and the mean in the control group. ($Z_i = (X_i - Z_{con})/SD_{con}$ where Z_i is the individual *Z*-score of the *i*th patient, X_i is the individuals test raw score, Z_{con} is the mean test result of the control group, and SD_{con} is the mean SD of the control group.) To correlate the NP test results with other findings, we used Pearson's correlation coefficient for continuous data and Mann–Whitney test for categorical data.

The four NP tests consisted of 23 subtasks, and a sumscore was calculated expressing the number of NP subtasks with scores ≤1 SD from the mean in the control group (range 0–23). The sumscores were then categorized into three groups: normal, 1–5 (≤1 SD from the mean sumscore in the control group); deficit, 6–8 ($>1 - \leq 2$ SD from the mean sumscore in the control group); and impairment, 9–23 (>2 SD from the mean sumscore in the control group).

Missing data were dealt with by imputing the mean score from the respective patient or control group. If the scores were missing because of inability to perform the test at hand, by imputing the lowest obtained score in the respective group. Four patients missed in average 2.5 of the 23 subtasks, and four controls missed on average 1.5 of the 23 subtasks.

Results

Mean NP test results are presented in Table 2. None failed on the CVLT long delay forced-choice recognition, indicating adequate test effort in all participants.

Table 2 Neuropsychological test results in patients treated for Lyme Neuroborreliosis (n = 50) and controls (n = 50). Numbers are raw scores (standard deviation)

Function	Measure	Patients	Controls	P-value
Executive	TMT 1 (s)	24.8 (8.6)	23.1 (7.1)	0.476
Functions	TMT 2 (s)	39.0 (18.2)	34.8 (14.1)	0.202
	TMT 3 (s)	46.9 (38.6)	39.2 (21.5)	0.146
	TMT 4 (s)	101.4 (55.1)	101.9 (46.3)	0.332
	Stroop 1 (s)	31.6 (7.4)	30.6 (6.8)	0.558
	Stroop 2 (s)	23.0 (4.9)	22.0 (3.7)	0.312
	Stroop 3 (s)	64.8 (24.1)	59.2 (17.6)	0.102
	Stroop 4 (s)	77.6 (30.1)	67.0 (16.3)	0.015*
Processing speed	Digit symbol (number of symbols)	41.8 (12.8)	45.5 (11.5)	0.060
	TMT 5 (s)	28.4 (9.7)	19.2 (6.7)	0.004*
Visual memory	Digit symbol, free recall (number of symbols)	6.6 (1.6)	7.2 (1.3)	0.038*
	Digit symbol, cued recall (number of symbols)	9.7 (4.7)	10.6 (4.6)	0.261
Verbal memory	CVLT trail 1 (number of words)	5.72 (1.9)	5.58 (2.0)	0.845
	CVLT trail 2 (number of words)	8.18 (2.4)	8.86 (2.7)	0.206
	CVLT trail 3 (number of words)	9.44 (2.4)	9.96 (2.8)	0.443
	CVLT trail 4 (number of words)	10.24 (2.1)	11.12 (2.6)	0.094
	CVLT trail 5 (number of words)	11.02 (2.4)	11.46 (2.6)	0.412
	CVLT trail 1-5 (number of words)	44.60 (9.1)	46.98 (11.5)	0.295
	CVLT list B (number of words)	4.68 (1.9)	5.50 (2.0)	0.014*
	CVLT Short delay (number of words)	9.36(3.4)	10.18 (3.1)	0.255
	CVLT Short delay cued (number of words)	11.58 (2.5)	11.33 (4,00)	0.780
	CVLT Long delay (number of words)	10.34 (3.4)	11.14 (3.1)	0.426
	CVLT Long delay cued (number of words)	11.50(3.4)	11.66 (3.4)	0.780

TMT, Trail Making Test. CVLT, California Verbal Learning Test. *Significance level $P < 0.05$.

Mean scores on tests assessing attention/executive functions (Stroop 4), processing speed/response speed (TMT 5), visual memory (digit symbol recall), and verbal memory (CLVT list B) were lower amongst LNB-treated patients than amongst matched controls. More patients than controls scored ≤1 SD of the mean in the control group on processing speed (TMT 5) and visual memory (digit symbol recall), 14 vs. 7 (P = 0.046) and 10 vs. 3 (P = 0.038), respectively.

Figure 1 shows mean Z-score in each NP test.

Figure 2 shows the distribution of sumscores in patients and controls.

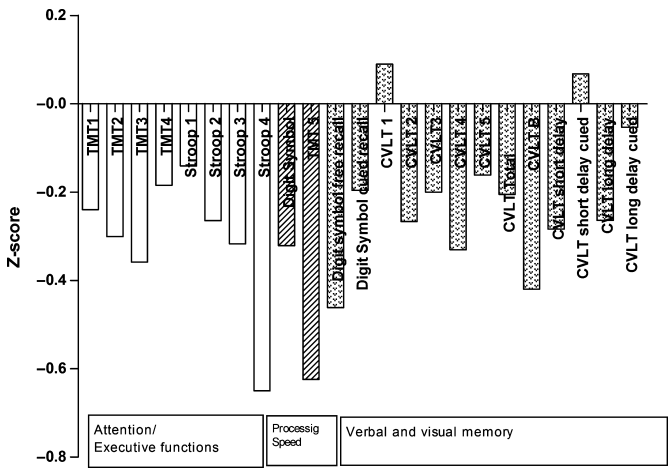
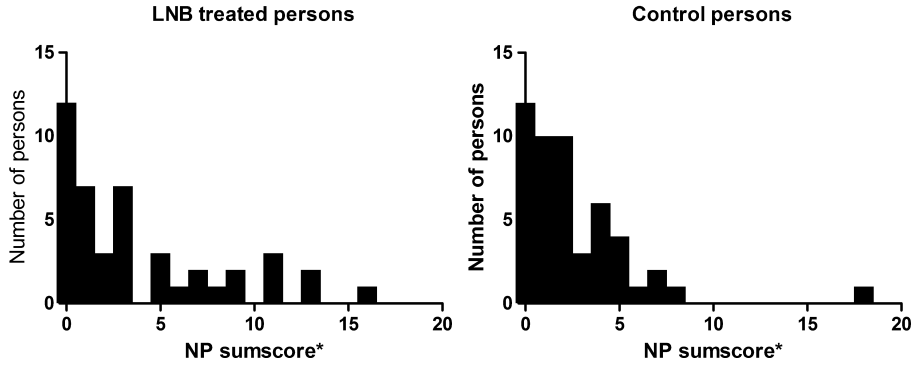


Figure 1 Patients neuropsychological test results displayed as z-scores, i.e. standard deviation above or below the mean in the control group. Y = 0 is mean in control group. TMT, trail-making test; CVLT, California Verbal Learning Test.



NP sumscore* categories	Patients n = 50	Controls n = 50	P-value
Normal 0–5 (≤1 SD from mean sumscore in the control group) n (%)	38 (76)	45 (90)	0.067
Deficit 6–8 (>1–≤2 SD from mean sumscore in the control group) n (%)	4 (8)	4 (8)	1.000
Impairment >8 (> 2 SD from mean sumscore in the control group) n (%)	8 (16)	1 (2)	**0.014**

Figure 2 Differences in neuropsychological (NP) sumscores in LNB treated patients and controls. NP sumscore, number of NP subtasks with scores ≤1 SD from the mean in the control group (range 0–23). Mean sumscores (SD), LNB treated patients 3.9 (4.2) and Controls 2.6 (3.1).

Correlations between NP test results, self-perceived symptoms, and occupational functioning are shown in Table 3.

We found no correlation between NP test results and fatigue (self-reported fatigue and FSS score), depression, subjective reported malaise, or HRQoL in the LNB-treated patients.

Discussion

We found that mean scores on four NP subtests assessing attention/executive functions (Stroop 4), processing speed (TMT 5), visual (digit symbol-free recall) and verbal (CVLT list B) memory were lower amongst European patients treated for LNB 30 months earlier than amongst matched controls. These findings indicate some dysfunction in these NP domains after treated LNB. To obtain a better understanding of the distribution and degree of NP dysfunction amongst our LNB-treated patients, we looked more detailed into the individual scores. In NP terms, scores worse than one SD from the mean in a control group are often considered as deficits, whilst scores worse than two SD are considered impairments. Analyses based on this assumption showed that more LNB-treated patients than controls obtained a score in accordance with an NP deficit on TMT 5 and on digit symbol-free recall test. Furthermore, we calculated an NP sumscore and categorized into groups based on one and two SD from the mean in the control group. The proportion of patients and controls with sumscores within one SD (defined as normal) and between one and two SD (defined as deficit) were similar, but more LNB-treated patients than controls had a sumscore more than two SD from the mean (defined as impairment). The results from the sumscore analyses illustrate that there is a wide range of performance on the NP tests in both patients and controls and that the vast majority of LNB-treated patients recover to an NP function comparable with the normal population. However, a small subgroup has a debilitating long-term course with some NP dysfunction.

The pattern of NP deficits amongst our LNB-treated patients was characterized by reduced impulse control and processing speed and poorer ability to verbal learning. Daily life consequences of these deficits may be reduced the ability to quickly perform a given task or come up with a solution to a given problem. Reduced learning and remembering of verbal material after just one presentation may cause problems recalling messages and information from lectures or discussions.

Earlier studies have not found a convincing cognitive deficit profile after LNB [4], and results from various tests in different studies are deviating. Some previous studies have, in contrast to ours, revealed deficits on the TMT 1–4 subtasks assessing attention/executive functions, [8,12,18], but deficits on TMT 5 assessing processing speed are also reported in accordance with our findings [8]. Pollina *et al*. [19] showed that performance on tasks like the TMT 5 and digit symbol could not be

Table 3 Correlation between NP test results and self-perceived function and occupational function in LNB-treated patients

	TMT5		Stroop 4		Digit symbol-free recall		CVLT list B	
Subjective reported functioning	Seconds Mean (SD)	*P*-value	Seconds Mean (SD)	*P*-value	Symbols recalled Mean (SD)	*P*-value	Words recalled Mean (SD)	*P*-value
Memory problems								
Yes $n = 23$	24.4 (7.0)	0.064	88.5 (35.4)	0.023*	6.3 (2.0)	0.296	4.4 (1.4)	0.489
No $n = 27$	22.5 (11.5)		68.3 (21.2)		6.9 (1.2)		4.9 (2.2)	
Concentration problems								
Yes $n = 17$	23.1 (18.7)	0.984	79.5 (27.0)	0.407	7.8 (1.3)	0.834	4.8 (1.7)	0.583
No $n = 33$	23.5 (10.3)		76.6 (32.0)		6.5 (1.7)		4.6 (2.0)	
Recovery								
Yes $n = 28$	20.1 (6.4)	0.014*	75.4 (31.5)	0.353	6.4 (1.8)	0.358	4.6 (2.2)	0.904
No $n = 22$	27.1 (11.5)		27.6 (11.5)		6.9 (1.3)		4.7 (1.6)	
Out of work because of post-LNB								
Yes $n = 5$	30.4 (17.1)	0.253	83.6 (33.4)	0.683	7.0 (1.6)	0.660	4.7 (1.9)	0.296
No $n = 45$	22.6 (8.4)		70.9 (30.0)		6.6 (1.6)		4.2 (2.3)	

TMT, trail-making test; CVLT, California Verbal Learning Test; LNB, Lyme neuroborreliosis; NP, neuropsychological.
*Significance level $P < 0.05$.

explained by sensory, perceptual, or motor deficits and could thus be interpreted as a specific impairment in processing speed. In a study of patients with symptomatic post-Lyme disease, Keilp *et al.* [10] found mild levels of impairment in processing speed and memory, correlated for intelligence (IQ). Other studies have reported more severe deficits in verbal memory than we did. Benke and Shadick reported problems with both short- and long-time verbal memory in patients with LNB [8,12], whilst Kalish did not [9]. Twenty patients with LNB in a European study were similar to our cohort on several variables, but they reported more extensive verbal-, but not visual memory problems [12]. A recent study of adolescents showed more visual than verbal memory problems like we did in adults [6], and this suggests that the verbal memory is more robust and less affected by LNB. The diversity in study results could partly be explained by the difference in patient selection criteria [7,8,19–21].

When comparing the NP results to HRQoL, subjective memory and concentration problems, subjective incomplete recovery, and self-reported reduced occupational function owing to post-LNB, the only correlations were between low scores on tasks assessing inhibition (Stroop 4) and subjective memory problems and low scores on processing/response speed (TMT-5) and subjective incomplete recovery. These findings are difficult to explain, but we know from other studies that subjective reported functioning does not always correlate with the objective findings [15]. Possible explanations may be that patients interpret attention and impulse control problems as memory problems. Awareness of deficits is probably also influenced by the individual demands at work and daily life and dependent of individual skills and ability to compensate. Overlapping NP tests could have given a more reliable cognitive profile in our study, but because of the time aspect, we chose test that assesses different aspects of cognition.

The underlying pathogenesis of post-Lyme syndrome and associated cognitive deficits is unknown. Amongst the theories discussed are sequelae after the initial bacterial damage, a post-infectious autoimmune reaction, a not completely eradicated infection, co-infection, or psychiatric comorbidity [22]. Earlier imaging studies have not revealed findings in the central nervous system that explain the cognitive deficits, but Fallon found more abnormalities in temporal, parietal, and limbic areas in a study of cerebral blood flow and metabolic rate in persistent Lyme encephalopathy patients as compared to controls [23]. Another study found a correlation with low test scores on memory and visuospatial organization and flow reductions in white matter index, particulary in the posterior temporal and parietal lobes bilaterally when doing NP tests simulatously with measuring Xenon(133)-regional cerebral blood flow [24]. Studies have shown that additional antibiotics after treated LNB may only have transient effects on long-term complaints, and persistent ongoing infection is thus unlikely an explanation of these problems [11,15,25,26]. In a previous publication, we have shown that mean score on MADRS amongst our patients did not indicate depression as a reason for the dysfunction [3], and co-infections with other tick-borne diseases do not seem to play a role.

Limitations of our study are the non-blinded testing and lack of matching regarding intelligence. We tried to minimize these problems by having a neuropsychologist

who was blinded to group adherence score the tests and by matching the patients and controls for demographic variables like age, educational level, and geographical region, known to correlate to some degree with intelligence [27]. The fact that the patients chose their controls in their own surroundings will also make the groups more comparable regarding IQ.

Restriction of patient recruitment to one geographical region can cause selection bias, but this is unlikely in this study as the clinical scores and measured improvements did not differ between the included and not included patients from the treatment trial. We did not correct for multiple comparisons with the Bonferroni correction method as we regard this as too conservative in this study where the variables are not independent of each other and can lead to missing real differences as suggested by Bland and Altman [28]. Strengths of our study are the well-characterized patients and the controlled design. We also analyzed factors that could potentially influence NP test performance as age, educational level, coexisting diseases, fatigue, malaise, and depression, but found no correlation between NP test performance and these factors. Some earlier studies have found a correlation between cognitive slowing and fatigue in patients with post-LNB [7], others have not [20,29]. Further investigation on pathogenesis and outcome in European LNB are warrnated.

Conclusion

Patients treated for LNB 30 months earlier scored lower on four NP subtasks assessing processing/response speed, visual and verbal memory, and executive/attention functions as compared to matched controls. Most LNB-treated patients performed comparable to the controls on NP testing, whilst a subgroup of patients had a debilitating long-term course with cognitive impairments. The NP test performances were not influenced by malaise, fatigue, or depression.

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Disclosure of conflict of interest

The authors declare no financial or other conflict of interests.

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