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Memory and Executive Functions in Adolescents with Posttreatment Lyme Disease

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Although adults with late stage posttreatment Lyme disease often experience difficulties in memory, little is known about the relationship between cognition and Lyme disease in children and adolescents. Twenty-five adolescents with late stage posttreatment Lyme disease (symptoms >6 months) and 25 participants without Lyme disease (matched on gender, IQ, age, socioeconomic status) were assessed for neuropsychological functioning, depression, school functioning, and predisease academic achievement. The Lyme group had significant deficits in cognition (short-term visual memory, short-term and delayed verbal memory, all forms of recognition memory), as well as worse attendance, grades, and subjective reports of memory problems, without differing in predisease achievement or depression. Deficits in visual memory exceeded deficits in verbal memory—a striking difference from what is reported in adults. These results reveal that adolescents with a history of treated Lyme disease are at risk for long-term problems in cognition and school functioning.

Key words: *adolescents, cognition, lyme disease, neuropsychology*

Lyme disease, caused by the tickborne bacterium *Borrelia burgdorferi* (Bb), can progress from an initial skin infection, to a disseminated infection, to a disabling multisystemic illness that can include dermatologic, arthritic, ophthalmologic, cardiac, psychiatric, and neurological manifestations. The primary aim of this study is to understand the impact of Lyme disease on adolescents in the area of memory and executive functioning. Lyme disease can be highly disruptive to adolescents, who need to meet the daily academic, emotional, and cognitive challenges of school. Some students who become ill with Lyme disease can no longer attend school on a regular basis, or they suddenly experience a sharp decline in academic achievement. The extent to which cognitive difficulties associated with Lyme disease occur is an area of great controversy and is especially difficult to evaluate without specialized neuropsychological instruments. At one end of the spectrum are those who think that Lyme disease is significantly underdiagnosed, extremely difficult to treat, and connected to serious long-term medical and cognitive consequences (Stricker, 2007). At the other end of this spectrum are those who think that Lyme disease is a faddish diagnosis of a disease that only occurs rarely, is easily treated, and is a magnet for those who may be emotionally maladjusted and seeking a medical explanation for psychiatric difficulties (Feder et al., 2008; Shapiro, 2008). The treatment offered an individual with Lyme disease is dependent on where on this continuum their health care provider, educator, or psychologist falls.

More than 21,000 cases of Lyme disease are reported annually, with the highest prevalence occurring in northeastern states (CDC, 2008). Neurological involvement

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associated with Lyme disease can take many forms, and the pathophysiology is not well understood. Bb can cause inflammation of nerves, which disrupts function. Both the central nervous and peripheral nervous systems can be involved. Manifestations of the disease may be caused directly by the spirochete itself or indirectly by the inflammatory response to the presence of the spirochete. When the brain becomes infected, macrophages—cells involved in the immune response—respond in part by releasing neurotoxins, including quinolic acid. Quinolic acid stimulates neurons to depolarize rapidly, which can cause the neurons to demyelinate and die. Perides, Tanner-Brown, Eskildsen, and Klempner (1999) have shown that those patients with Lyme disease have an increased production of an enzyme called matrix metalloproteinases (MMPS), which can degrade support tissues of blood vessels. It may be implicated in the breakdown of the blood-brain barrier.

Objective neurological involvement has been estimated to occur in 5% of people who become infected with Bb and remain untreated (CDC, 2008). Lyme borreliosis may affect the nervous system in a number of ways: typicalpresentation is a (weakness in muscular tone) triad of symptoms that includes encephalitis, meningitis, and cranial neuritis (Halperin et al., 2008). Symptoms of encephalitis and meningitis, which may appear suddenly, often include high fever, severe and persistent headache, stiff neck, nausea, and vomiting. Other less frequent symptoms may include confusion, mood lability, irritability, and poor sleep. The third symptom that indicates neurological involvement is cranial neuritis. Of the cranial nerves, the VII is most commonly involved, causing a facial palsy—a drooping of one side of the face, with a decreased ability to move the face. Less frequently symptoms include radiculitis (inflammation of the root of the spinal nerve), peripheral neuropathies (shooting or stabbing pains), burning pains, and parathesias (Logigian, 1997). Parathesias are abnormal neurological sensations that include numbness, tingling, burning, prickling, and hyperthesia (increased sensitivity) (Pachner & Steere, 1985). See Table 1 for a summary of symptoms of Lyme disease.

Neurological involvement associated with Lyme infection does not need to be specific or severe. Halperin (1988) also reports that encephalopathy is another neurologic sign in adults with Lyme disease. Encephalopathy describes any significant changes in mental state and can include forgetfulness, behavioral changes, confusion, memory problems, and changes in mood.

Studies that have examined the impact of Lyme disease on cognition in adults have produced different results on similar measures because of the variability of participant inclusion criteria, assessment tools used, and study design. When deficits appear, one area of functioning that seems to be spared is verbal IQ—as measured by the various versions of the *Wechsler Adult Intelligence Test* (WAIS; Bloom, Wyckoff, Meissner, & Steere, 1998; Halperin et al., 1988; Keilp et al., 2006; Krupp et al., 1991). In contrast, the ability to attend to and remember new verbal and nonverbal information (*California Verbal Learning Test or Selective Reminding Test*) seems to be compromised, although evidence is far from complete or consistent (Benke, Gasse, Hittmair-Delazer, & Schmutzhard, 1995; Halperin et al., 1988; Krupp et al., 1991; Logigan, Kaplan, & Steere, 1990; Shadick et al., 1994). Visual spatial processing (*Wechsler Performance IQ and/or Block Design subtest*) has been impaired in some studies (Keilp et al., 2006) and not impaired in others (Benke et al., 1995; Krupp et al., 1991). Fine motor abilities (*Purdue Pegboard*) also have been found to be impaired (Guadino, Coyle, & Krupp, 1997; Halperin et al., 1998; Shadick et al., 1994). Working memory and executive functioning abilities have been explored through the use of single subtests or composite scores (*Booklet Categories Test, Trail-Making Test, Symbol Digits Modalities, Wechsler Memory Scale-R Attention Concentration Index, Verbal Fluency Measures*) (Bloom, Wyckoff, Meissner, & Steere, 1998; Gaudino et al., 1997; Halperin et al., 1988; Kaplan, Meadows, Vincent, Logigian, & Steere, 1992; Krupp et al., 1991) but never have been comprehensively assessed.

Less is known about the impact of Lyme disease on cognition in children and adolescents. Participants in a

TABLE 1
Symptoms of Lyme Disease and Persistent Sequelae

Encephalitis and meningitis manifest as one or more of the following:
Most frequently and often with sudden onset:
Persistent fever
Severe and persistent headache
Stiff neck
Nausea and vomiting
Less frequently:
Confusion
Mood lability
Irritability
Poor sleep
Cranial neuritis, most often VII, manifests as one or more of the following:
Facial palsy
Peripheral neuropathies (e.g., shooting, stabbing pain)
Burning pains
Parathesias (e.g., numbness, tingling, burning, pinching, increased sensitivity)
Encephalopathy manifests as one or more of the following:
Forgetfulness
Behavioral changes
Confusion
Memory problems
Changes in mood

Table based on Halperin et al. 2008; Logigian 1997; and Pachner & Steere 1985.

Lyme disease study who were identified early and treated adequately had intact cognitive abilities both in the short and the long term (Adams, Rose, Eppes, & Klein, 1994, 1999). Only one study (Tager et al., 2001) has used standardized tests of cognition on a group of adolescents identified and treated for Lyme disease for more than six months and compared testing results to those of a matched group. Results of that study indicate that adolescents with Lyme disease had great difficulty completing tasks that were loaded heavily on visual spatial abilities and had more difficulty remembering new visual and verbal information in the short term. Verbal IQ, as with adults, was spared. Findings also suggested that visual and verbal memory, working memory and executive functioning (*Wide Range Assessment of Memory and Learning, Wisconsin Card Sorting Test*) could be areas of weakness in children and adolescents with Lyme disease. However, Tager's study (Tager et al., 2001) had a small sample size, did not control IQ or socioeconomic status (SES), and used selected subtests rather than a comprehensive assessment of memory and executive functions. The adolescents with long-term Lyme disease in Tager's study were preselected based on the reports of cognitive deficits, thus biasing the sample toward finding problems, and there was no assessment of subjective feelings of cognitive difficulty. In addition, most studies conducted did not have examiners that were blind to the study condition, and no study has compared current academic functioning and school attendance while controlling for predisease achievement. The following study was designed to gain a better understanding of the cognitive status of adolescents with, late-stage posttreatment Lyme disease by addressing these limitations of previous studies.

Hypotheses

Hypothesis 1

Adolescents with late-stage posttreatment Lyme disease subjectively experience greater overall memory difficulties than matched comparisons. They also obtain lower scores on objective tests of memory—including verbal, visual and attention/concentration short-term memory, long-term retrieval, and recognition memory—than matched comparisons.

Hypothesis 2

Adolescents with late-stage Lyme disease will experience difficulties in the executive functioning areas of verbal fluency and spatial planning compared to matched comparisons. Specifically, they will obtain lower scores on the *Phonemic Letter Fluency* subtest and the overall achievement score on the *Tower Test* from the Delis Kaplan Executive Functions System (DKEFS) than matched comparisons.

Hypothesis 3

Adolescents with Lyme disease will have increased difficulty in school performance—as measured by lower grade point average (GPA) and school attendance in the fall semester of the year in which the data were collected—than matched comparisons. Lower academic performance will not be as a result of lower predisease academic functioning or depressive symptomatology.

METHODS

Participants

Participants were 25 adolescents between the ages of 13 and 18, with late-stage posttreatment Lyme disease, and 25 comparisons matched on age, gender, IQ, and SES (see Table 2). Although race was not an intentional part of the study design, all participants were Caucasian; only members of this ethnic group responded to the recruitment of participants with Lyme. To be considered a match, comparison group participants had to be within six months of age, in one of three family income ranges ($0–25,000; $25,001–50,000; or $50,000), and within 10 points of a Lyme group participant on the Full Scale IQ (FSIQ) from the *Wechsler Abbreviated Scale of Intelligence* (WASI; Wechsler, 1999). Parents of potential participants were screened on the phone to collect history and to determine whether they met basic inclusion criteria. Approximately every fourth adolescent screened met criteria for participation in the study. The typical reason for study exclusion was that the adolescent did not meet the serologic criteria for the diagnosis of Lyme disease specified by the Centers for Disease Control (CDC, 2008). In a follow-up meeting, Verbal IQ (VIQ) measures (controls) and medical documentation (Lyme group) were collected to confirm group membership prior to administering the neuropsychological battery.

Inclusion criteria for the Lyme group consisted of the following: (a) a historical serological confirmation of exposure to an agent of Lyme disease, using the 2001 Centers for Disease Control serological criteria (an equivocal or positive enzyme-linked immunoassay (ELISA) and a positive IgM or IgG Western Blot) or (b) at least one medically documented Erythema migrans (EM) rash (CDC, 1995), and (c) participants must have received a diagnosis of Lyme disease between six months and four years prior to participation in the study. All Lyme group participants received antibiotic

TABLE 2
Sample Characteristics ($n = 50$)

	Lyme Mean (SD)	*Comparisons Mean (SD)*	*t*	η^2
Age (years–months)	16–2 (2–1)	15–9 (1–8)	.80	.013
WASI				
Full Scale IQ	108.0 (7.5)	108.8 (7.3)	−.42	.004
Verbal IQ	109.9 (9.9)	111.9 (11.1)	−.70	.010
Performance IQ	104.5 (7.3)	103.2 (6.6)	.69	.009

	n	*percentage*	*n*	*percentage*
Gender				
Male	11	22	11	22
Female	14	28	14	28
Socioeconomic Status				
$25,000–50,000	2	4	2	4
Above $50,000	23	46	23	46
Body Mass Index				
5th–85th Percentile	24	48	23	46
85th–95th Percentile	1	2	2	4

Characteristics of Lyme Group ($n = 25$)	*n*	*Percentage*
Intravenous Treatment		
Currently	5	20
Past	8	32
Never	12	48
Coinfections		
Yes	7	28
No	18	72
Homebound Tutoring		
Presently	6	24
Past	5	20
Never	14	56

	Mean	*SD*	*Range*
Months Since Diagnosis	24.6	12.12	6–48

treatment for Lyme prior to participation in the study. Control group participants had no medical history of Lyme infection or a Lyme-like illness according to parent report. Exclusion criteria included histories of clinically significant prior medical, neurological, or psychiatric problems that might compromise cognitive functioning. These problems included but were not limited to history of seizure disorder, head trauma with loss of consciousness, Attention Deficit Hyperactivity Disorder, substance abuse, or a learning disability. Exclusion criteria were assessed at the time of the phone screening.

Measures

The WASI

The WASI (Wechsler, 1999) provides an estimate of an individual's VIQ, nonverbal IQ (PIQ), and general cognitive functioning, or FSIQ. According to the manual, the correlations of the FSIQ of the WASI with the FSIQ of the *Wechsler Adult Intelligence Scale-Third Edition* (WAIS-III; Wechsler, 1997) and the FSIQ of the *Wechsler Intelligence Scale For Children-Third Edition* (WISC-III; Wechsler, 1997) are .92 and .87, respectively.

Wide Range Test of Memory and Learning-Second Edition (WRAML-II)

The WRAML-II (Adams & Sheslow, 2005) is a widely used, standardized test that assesses the ability to learn and remember different types of information. Individual subtests yield the following indices: General Memory, Verbal Memory, Visual Memory, Attention/Concentration, and Long-Term Retrieval. The WRAML-II also assesses recognition of previously presented information. Index scores in this area include General Recognition, Verbal Recognition, and Visual Recognition. Coefficient alphas for this sample were .82 (Verbal Memory Index), .79 (Visual Memory Index), .83 (Attention/Concentration Index), and .77 (General Recognition Index).

DKEFS

The DKEFS (Delis, Kaplan, & Kramer, 2001) is a set of standardized tests that assess component processes of key executive functions in verbal and visuospatial modalities. Subtests included the *Phonemic Verbal Fluency Test*, a measure of the strategic organization of verbal output in terms of categories of phonemic characteristics, alpha = .76, and the *Tower Test*, the overall achievement score, alpha = .48. Abilities needed for success on the latter task include visual attention, visual-spatial skills, spatial planning, rule learning, inhibition of perseverative and impulsive responding, and the ability to establish and maintain the instructional set. These two subtests were selected for administration because prior research indicated the areas tested were likely present cognitive difficulty for those with long-term Lyme disease.

Reynolds Adolescent Depression Scale (RADS)

The RADS (Reynolds, 1987) is a reliable and valid self-report measure of depressive symptoms. Adolescents are asked to mark the 30 test questions according to how they feel, using a 4-point Likert response format (never, hardly ever, sometimes, most of the time). Total scores range from 30–120; 77 or greater is the cutoff score associated with possible clinical depression. Four individual components of depression are evaluated: Dysphoric Mood, Anhedonia/Negative Affect, Negative Self-Evaluation, and Somatic Complaints (alpha = .74 for Total Score). The Somatic Complaints

subscale includes two items of clinical importance: item 18, "I feel tired" and item 24, "I have trouble sleeping." These two items were analyzed separately to examine the potentially confounding effects of fatigue and sleep deprivation on neuropsychological test performance.

Self-Report of Cognitive Ability

A measure of subjective cognitive difficulties was also included in order to compare the adolescents' perceptions with objective findings, as well as capturing an estimate of quality of life and self-awareness. Measuring patients' subjective experience of disease and comparing it with objective data are in concert with the National Institute of Health's "Bench to Bedside" initiative, which was designed to integrate patient presentations faced by clinical practitioners and investigators with those of basic scientists (National Institutes of Health, 2006). Participants rated their own degree of cognitive complaints by completing a Likert scale to this prompt: "Please rate your current difficulties in thinking, concentrating, and memory." Responses included 1 (No Difficulty), 2 (A Little Difficulty), 3 (Some Difficulty), 4 (Significant Difficulty), and 5 (Severe Difficulty).

Academic Performance Scores

Current GPA was calculated for the first two semesters of the participant's current school year by assigning numerical weights for letter grades in core academic subjects (English, social studies, math, and science). Grades in the A range were given a 4, B range a 3, C range a 2, D range a 1, and F range a 0. Courses that were not completed because of illness were assigned a 0 point value. School attendance was calculated by reviewing attendance profiles and counting the number of excused days from school from August 28 through December 31 of the 2005–2006 school year. There were very few unexcused absences in this group. Group administered, standardized test data from elementary school in reading and math were gathered as well, to estimate predisease functioning. Although tests used varied by state, all states reported normal curve equivalents for global reading and global math, allowing for comparisons across tests. Examples of standardized achievement tests used in this study are the *Stanford Achievement Test*, *California Test of Basic Skills*, and *New York State State-Wide Testing Program Achievement Tests*.

Data Analytic Plan

As part of the data analytic plan, *t*-tests were run to ensure that the Lyme group participants did not differ from comparisons on matching variables (age, IQ, gender, SES) or covariates that might account for cognitive differences or school performance in the two groups (i.e., depression, predisease achievement scores, body mass index [BMI]). Within the Lyme group only, participants with a history of receiving intravenous antibiotic treatments or with a coinfection such as erlichiosis, babesiosis, or bartenella were compared with those participants without such a treatment history or coinfection on overall IQ, depression, memory, or executive functioning. To reduce Type 1 error, MANOVAs were performed on general memory difficulty, using self-ratings and the WRAML-II General Memory Index. If that MANOVA revealed significant differences in the predicted direction between groups, further MANOVAs would be performed on the short-term memory indices (WRAML-II Visual Memory, Verbal Memory, Attention/Concentration) and on the Recognition Memory Indices (visual, verbal), as well as a repeated measures MANOVA to determine significant differences in time (immediate recall versus delayed recall), group status (Lyme versus comparisons), or an interaction of the two on the *Story Memory and Verbal Learning* subtests—the only two subtests on the WRAML-II that include a delayed-recall component. If the omnibus tests were significant, independent samples *t*-tests were performed on specific indices or subtests. A separate MANOVA examined differences between the Lyme and comparison group on measures of executive functions (DKEFS *Letter Fluency* and *Tower Achievement* tests). A final MANOVA was performed on measures of academic performance (GPA, missed school days).

RESULTS

Sample Characteristics

There were no significant differences between the Lyme and comparison group on the matching variables of gender, age, SES, and IQ. The average age of Lyme participants was 16 years, 2 months; the average age for the control group was 15 years, 10 months (Table 1). The Lyme group had an average FSIQ of 108.0 and the comparison group, 108.8. Males accounted for 44% of the sample, and 92% of the sample had family incomes above $50,000 and 8% between $25,001 and $50,000. Overall physical health was estimated by calculating each participant's BMI score based on height and weight: 94% of the participants had a BMI between the 5th and the 85th percentile, considered a healthy weight; 6% had a BMI between the 85th and 95th percentile, considered at risk for being overweight. The groups did not differ on BMI. One Lyme group participant became so fatigued by testing that she was only able

to complete IQ and Executive Functions testing but not the WRAML-II, lowering the overall sample size to 49 on the WRAML-II.

Characteristics of Lyme Group Participants

The average number of months between diagnosis and testing for participants with Lyme disease was 24.6 months (*SD* 12.12 months). Thirteen participants with Lyme disease (52%) had received either current or past intravenous antibiotic treatment for Lyme disease. In addition to providing evidence of a diagnosis of Lyme disease, 7 participants (28%) also provided serological evidence of tickborne coinfections such as babesia, bartonella, or erlichiosis. The remaining 18 participants with Lyme disease (72%) either had negative serology or no evidence for coinfections or they had no evidence for the presence of a coinfection. Forty-four percent of the Lyme participants had received past or current home instruction provided by their schools. Home instruction is provided to students who are too sick to attend school on a regular basis. No control group participants had ever received home instruction.

Potential Covariates

Overall depression scores on the RADS fell in the average range for the Lyme group ($M = 52.2$, $SD = 8.3$) and did not significantly differ from overall depression scores for the comparison group ($M = 47.9$, $SD = 8.2$), $t(48) = 1.9$, $p = 06$, $\eta^2 = .071$. The groups did differ on the number of somatic complaints experienced, with the Lyme group ($M = 57.6$, $SD = 7.4$) having significantly more complaints than the comparison group ($M = 49.5$, $SD = 10.5$), $t(48) = 3.1$, $p = .003$, $\eta^2 = .170$. Because severe fatigue and lack of sleep have profound impact on cognitive functioning, especially in the areas of attention, working memory, higher-order language skills, and executive functioning in adults (Harrison & Horne, 1998) and children (Sadah, Gruber, & Raviv, 2002), two items from the RADS Somatic Complaints cluster (item 18, ''I feel tired,'' and item 24, ''I have trouble sleeping'') were analyzed separately. The groups did not differ in amount of fatigue reported, although both groups endorsed a significant amount of fatigue (Lyme group: $M = 3.48$, $SD = .82$, comparison group: $M = 3.00$, $SD = .91$, $t(48) = 3.8$, $p = .057$, $\eta^2 = .074$). The groups did differ in amount of sleeplessness reported, with the Lyme group ($M = 3.04.6$, $SD = 1.06$) reporting more complaints than the comparison group ($M = 2.24$, $SD = 10.5$), $t(48) = 6.9$, $p = .01$, $\eta^2 = .126$. An examination of the correlation between item 24 and all dependent variables revealed that only the WRAML-II Attention/Concentration Index was significantly correlated with trouble sleeping. An ANOVA with group and RADS item 24 as independent variables and the Attention/Concentration Index as the dependent variable found no significant differences between the groups with item 24 in the equation, $F = (2, 49) = 2.971$, $p = .061$, $\eta^2 = .152$. Group administered standardized achievement tests scores (reported in Normal Curve Equivalents (NCEs) in reading and writing from fourth grade were collected from participants' school records in order to compare both groups' abilities prior to the onset of Lyme disease in the Lyme group. The Lyme group ($M = 75.2$, $SD = 18.9$) and the comparison group ($M = 80.4$, $SD = 14.7$) both scored in the high average range for reading abilities, $t(33) = -.87$, $p = .39$, $\eta^2 = .023$ and global math; Lyme group, $M = 76.2$, $SD = 16.3$; comparison group, $M = 78.9$, $SD = 18.4$, and did not differ from each other, $t(33) = -.44$, $p = .66$, $\eta^2 = .006$.

Correlations

Age and gender were not significantly correlated with outcome measures (see Table 3). Scores on the WASI FSIQ were correlated with measures of memory ability (WRAML-II General Memory Index, Verbal Memory Index, Attention/Concentration Index, General Recognition, and Visual Recognition), tests of executive functioning (Tower/Achievement), and academic functioning (GPA). Self-report of memory functioning was highly correlated with performance on objective measures of memory ability (WRAML-II General Memory Index, Verbal Memory Index, Visual Memory Index, Attention/Concentration Index, Verbal Recognition) and academic functioning (days missed, GPA). Performance on the WRAML-II's General Memory Index was correlated with all measures of memory, tests of executive functioning (Phonemic Verbal Letter Fluency, Tower/Achievement), and measures of academic functioning (days missed, GPA).

Memory Measures

Participants with Lyme disease (Table 4) rated themselves as having moderate difficulties in the area of memory ($M = 2.8$, $SD = 1.0$), whereas participants in the comparison group rated themselves as having little or no complaints ($M = 1.4$, $SD = .47$). Of the 50 participants, 2 (4%) participants in the Lyme group and 5 (10%) participants in the comparison group rated themselves as having no difficulty in memory; 6 (12%) Lyme group and 19 (38%) comparison group participants rated themselves as having a little difficulty; 12 (24%) Lyme group and 1 (2%) comparison group participants rated themselves as having some difficulty; 5 (10%) Lyme group participants rated themselves as having

TABLE 3
Correlations between Measures of Memory, Executive Functioning, and School Performance

	Membership		*Gender*	*WASI FSIQ*	*WASI VIQ*	*WASI PIQ*
	Group	*Age*				
Memory Measures ($n = 49$)						
Self-Report	−.58**	−.06	.21	−.15	−.26	.19
WRAML-II GMI	.56**	.13	−.04	.45**	.44**	.18
Verbal Memory	.36*	.07	.13	.30*	.31*	.11
Visual Memory	.66**	−.39	.05	.20	.17	.04
Attention/Concentration	.29	.26	−.20	.58**	.55**	.30*
General Recognition	.40**	.10	.13	.34*	.28	.23
Verbal Recognition	.35*	−.07	.08	.21	.24	.08
Visual Recognition	.34*	.18	.11	.38**	.27	.30
Executive Functions ($n = 50$)						
Word Fluency						
# of Words (Cond. 1)	−.02	.89	−.16	.27	.25	.15
Tower						
Achievement	.39**	.29	−.09	.39**	.21	.30*
Rule v. Ratio	.03	.09	−.24	.18	.02	.31*
Academic Measures ($n = 30$)						
Grade Point Average	.35*	.15	−.09	.42*	.44*	.14
Days Missed	−.45**	.27	.03	−.11	−.23	.24

	Self-Report/Memory	*WRAML-II GMI*	*RADS Overall Depression*	*RADS Somatic Complaints*	*Reading Achievement*	*Math Achievement*
Memory Measures						
Self-Report	1.0	−.41**	.33*	.26	.03	−.09
WRAML-II GMI	−.41**	1.0	−.34*	−.46**	.48**	.17
Verbal Memory	−.30*.	.75**	−.36*	−.39*	.47**	.11
Visual Memory	−.36*	.82**	−.27	−.36*	.15	.05
Attention/Concentration	−.29*	.71**	−.21	−.30	.70**	.31
General Recognition	−.22	.69**	−.15*	−.35*	.33	.04
Verbal Recognition	−.34*	.60**	−.08	−.23	.28	−.03
Visual Recognition	−.22	.57**	−.17	−.34*	.31	.04
Executive Functions						
Word Fluency						
# of Words (Cond. 1)	−.12	.29*	.01	−.01	.22	.20
Tower						
Achievement	−.27	.41**	−.30	−.28	.34	.41*
Rule v. Ratio	−.04	.03	.08	.05	.24	.15
Academic Measures						
Grade Point Average	−.54**	.45*	−.44*	.22	.37*	.34
Days Missed	.67**	−.27	.28	−.31	−.06	–

*Significant at the $p < .05$ level.
**Significant at the $p < .01$ level.

significant or severe memory problems, whereas none of the comparison group did. Performance on objective measures of memory functioning (WRAML-II) indicates average overall memory abilities in the Lyme ($M = 91.7$, $SD = 10.2$) and comparison ($M = 106.1$, $SD = 11.5$) groups, with the Lyme group significantly lower. A MANOVA, conducted to compare participants with and without Lyme disease on a self-report of memory difficulties and performance on the General Memory Index Score on the WRAML-II, showed highly significant differences in the predicted direction between subjects, $F(2, 46) = 2406.48$, $p < .000$, $\eta^2 = .991$. Significant differences were seen both on self-report measures, $F(1, 48) = 21.63$, $p < .000$, $\eta^2 = .33$, and the WRAML-II GMI score, $F(1, 47) = 21.48$, $p < .000$, $\eta^2 = .314$.

An subsequent MANOVA was conducted on the indices that comprise the General Memory Index Score on the WRAML-II. Adolescents with Lyme disease performed significantly worse on an overall estimate of short-term visual abilities, the Visual Memory Index, $F(1, 47) = 31.84$, $p < .000$, $\eta^2 = .40$. Participants with

TABLE 4
Performance by Groups on Measures of Memory and Executive Functioning

	Lyme (n = 24)		*Comparisons (n = 25)*			
	Mean	*SD*	*Mean*	*SD*	*t*	η^2
Self-Ratings	2.8	1.0	1.4	.47	4.7**	.311
WRAML-II Index Scores						
General Memory Index	91.7	10.2	106.2	11.5	−4.6**	.314
Verbal Memory Index	100.4	10.3	108.0	9.7	−2.6*	.130
Visual Memory Index	80.1	10.2	98.6	12.3	−5.6**	.404
Attention/Concentration Index	100.0	9.8	106.5	13.6	−1.9	.072
WRAML-II Verbal Subtests						
Story Memory	10.7	2.2	12.0	2.1	−2.1*	.086
Verbal Learning	9.6	1.9	11.0	2.4	−2.3*	.103
Story Memory Recall	10.3	2.4	12.0	2.0	−2.6*	.126
Verbal Learning Recall	9.0	2.2	11.5	2.4	−3.8**	.237
Verbal Working Memory	9.3	2.7	10.8	2.2	−2.3*	.098
WRAML-II Attention/Concentration Subtests						
Finger Windows	7.5	2.7	9.7	2.9	−2.7**	.138
Number Letter Sequencing	12.4	2.1	12.5	2.9	−0.2	.001
WRAML-II Visual Subtests						
Design Memory	6.5	1.7	10.0	2.7	−5.3**	.374
Picture Memory	7.1	2.5	9.6	2.2	−3.7**	.227
WRAML-II Recognition Index Scores						
General Recognition	93.4	12.4	103.4	11.4	−3.0**	.158
Verbal Recognition	99.7	10.5	106.2	7.4	−2.5*	.118
Visual Recognition	89.1	12.7	99.6	16.5	−2.5*	.116
DKEFS Verbal Fluency Test						
Letter Fluency	10.9	4.0	10.8	2.7	0.1	.001
DKEFS Tower Test						
Total Achievement	9.1	2.4	11.0	2.0	−2.6*	.150

*$p < .05$, **$p < .01$.

Lyme disease fell below the average range ($M = 80.1$, $SD = 10.2$), whereas comparison group performance fell within the average range ($M = 98.6$, $SD = 12.3$). Lyme disease participants performed more poorly on the Verbal Memory Index Score, $F(1, 47) = 7.03$, $p = .01$, $\eta^2 = .13$, even though both groups fell within the average range (Lyme group = 100.4, $SD = 10.3$; comparison group = 108.0, $SD = 9.7$). This visual/verbal split was also observable on the two subtests that comprise the Attention/Concentration Index; differences were in the predicted direction but did not reach statistical significance on the Index, $F(1, 47) = 3.64$, $p = .06$, $\eta^2 = .07$, but did on the visual subtest. Participants with Lyme disease performed in the low average range ($M = 7.5$, $SD = 2.7$) on *Finger Windows*, a test of visual attention, whereas participants in the comparison group performed in the average range ($M = 9.7$, $SD = 2.9$). On a test of verbal attention, *Number Letter Sequencing*, Lyme group participants ($M = 12.4$, $SD = 2.1$) and comparison group participants ($M = 12.5$, $SD = 2.9$) both performed in the high average range.

Another follow-up MANOVA revealed that adolescents with Lyme disease had significantly lower performance on a measure of overall recognition ability, General Recognition Index Score, $F(1, 47) = 8.81$, $p < .01$, $\eta^2 = .12$, as well as the two indices that comprise that score: Verbal Recognition Index, $F(1, 47) = 6.29$, $p = .02$, $\eta^2 = .12$, and Visual Recognition Index, $F(1, 47) = 6.19$, $p = .02$, $\eta^2 = .16$. Participants with Lyme disease were average on General Recognition Memory ($M = 93.4$, $SD = 12.4$), Verbal Recognition Memory ($M = 99.7$, $SD = 10.5$), and low average on measure Visual Recognition Memory ($M = 89.1$, $SD = 12.7$), whereas comparison group participants were average on all three measures: General ($M = 103.4$, $SD = 11.4$), Verbal ($M = 106.2$, $SD = 7.4$) and Visual ($M = 99.6$, $SD = 16.5$).

A repeated measures MANOVA was performed to determine significant differences from time (immediate versus delayed recall), group status (Lyme versus comparison groups), or an interaction of the two on the *Story Memory* and *Verbal Learning* subtests, the only two subtests on the WRAML-II that include a

delayed-recall component. Results reveal a significant difference between the Lyme and comparison groups on verbal measures overall, $F(2, 46) = 2406.48$, $p < .000$, $\eta^2 = .17$. Tests of within subject effects (time*group type) did reach statistical significance on the *Verbal Learning* subtest ($p = .03$), with the Lyme group performing more poorly over time.

Executive Functioning

Results from a MANOVA on the DKEFS revealed that adolescents with Lyme disease had significantly poorer performance on the *Tower* subtest, an estimate of spatial planning ability, $F(1, 48) = 8.49$, $p < .000$, $\eta^2 = .15$, but did not differ from comparisons in the number of errors produced on the *Tower* task and measures of phonemic verbal fluency., $F(1, 49) = 8.49$, $p = .005$, $\eta^2 = .15$.

Academic Achievement

Thirty-three out of the 50 participants' schools responded to requests for academic information (Lyme group = 20, comparison group = 13). A MANOVA on measures of school performance showed that participants with Lyme disease missed more days of school from September 1, 2005 to December 31, 2005 than the comparison group, $F(1, 29) = 5.76$, $p = .03$, $\eta^2 = .20$, and had a significantly lower GPA than comparison group participants, $F(1, 29) = 2.01$, $p < .01$, $\eta^2 = .01$. Participants with Lyme disease missed significantly more days of school ($M = 20.5$, $SD = 20.7$) than the comparison group members ($M = 4.7$, $SD = 3.2$), $t(32) = 2.6$, $p < .05$. Within the Lyme group, 8 (38.4%) participants missed 0–10 days of school, 7 (32.6%) missed 11–20 days, and 6 (28.8%) participants missed more than 20 days. In the comparison group, 13 participants (92.8%) missed 0–10 days of school: the remaining participant missed 11 days of school. Participants with Lyme disease had a current GPA in the C + range ($M = 2.9$, $SD = .80$) and the comparison group in the B + range ($M = 3.4$, $SD = .39$), $t(32) = -2.2$, $p < .05$.

DISCUSSION

This study examined memory, executive functioning, and school performance in a sample of adolescents with late-stage posttreatment Lyme disease and healthy matched controls. Previous studies in adults with late-stage Lyme disease have found neuropsychological difficulties in some, but not all, cases. The few studies that examined the relationship between Lyme disease and cognition in children and adolescents found no impairment in those children and adolescents who had been identified and treated early (Adams et al., 1994, 1999) but significant difficulties in children and adolescents with later-stage posttreatment Lyme disease (Tager et al., 2001).

The current study not only found that adolescents with late-stage posttreatment Lyme disease had an increased subjective experience of cognitive difficulties compared to adolescents without Lyme disease, but they also had significantly poorer performance across most domains of objective memory (verbal and visual memory in the immediate and long term, attention/concentration, and recognition memory), the executive ability of spatial planning, and on measures of current academic performance (GPA, missed days of school). Not all participants with a history of Lyme disease had the experience of significant difficulties with cognition (34% reported "some" to "significant" difficulty), but the subjective experience of cognitive difficulty was highly correlated with poorer performance on objective neuropsychological tests in the areas of memory and executive functioning, as well as poorer academic performance in school. On the WRAML-II, participants with posttreatment Lyme disease had significantly lower general memory scores compared to controls, as well as lower index scores in the areas of immediate verbal memory and visual memory. One of the most important findings of this study was the statistically and clinically significant difficulties in the area of visual memory that adolescents in the Lyme group experienced. As a group, adolescents with a history of Lyme disease performed more than 1 standard deviation below average on tests of visual memory, whereas adolescents without Lyme performed in the average range. Out of the 24 Lyme participants, 21 performed in the low average range or below, and 3 performed in the average range. In contrast, out of the 25 non-Lyme participants, 5 performed in the low average range or below, 16 performed in the average range, and 4 performed in the high average range or above.

Differences between the two groups on verbal memory tests were also present, but not as large. The subtests that comprise the WRAML-II Verbal Memory composite include a test in which a story needs to be remembered, as well as a list of words presented over several trials. As in the case of visual memory tests, the Lyme group performed significantly worse than the non-Lyme group on both individual subtests. In addition, Lyme participants performed more poorly on delayed-recall verbal tests and also on tests of working memory compared to matched controls.

The difference between verbal and visual performance was also seen on results relating to the Attention/Concentration Index on the WRAML-II. Although the two groups did not differ on the overall Index, differences were observed on one of the two individual subtests that comprise the Index. There were no

differences between groups on the verbally based test (*Number/Letter*), in which participants needed to remember increasingly longer series of numbers and letters, but significant differences were observed on the visually based test (*Finger Windows*), in which participants needed to remember increasingly longer series of visual patterns.

Results taken from the DKEFS also reflect the differences between visually and verbally based tasks seen on tests of memory performance. The two groups did not differ on a verbal executive task (phonemic verbal fluency), in which participants needed to generate as many words as possible based on an abstract category, but they did differ on a visually based executive functioning task (spatial planning). Out of the 25 participants in the Lyme group, 8 scored in the low average range or below, 15 scored in the average range, and 2 scored in the high average range or above. Out of the 25 non-Lyme participants, 2 scored in the low average range or below, 16 scored in the average range, and 7 scored in the high average range or above. On this test, participants must visualize steps in advance to move successfully from an initial pattern of discs (of varying sizes) on pegs to an ending pattern while following a set of rules. Participants who did poorly on the *Tower* tasks often did not thoughtfully plan their moves or appeared unable to visualize the moves needed to complete the task successfully; in the middle of the task, they would often move discs randomly from peg to peg in no seeming order.

The differences seen in self-assessment of cognitive ability and in significant difference on objective tests of memory and executive functioning are also seen in terms of real-life school performance. Adolescents with a history of Lyme disease had significantly lower GPAs and missed more days of school, for the first semester of the current school year, compared to adolescents without Lyme disease. Adolescents with posttreatment Lyme disease in this sample struggle to meet the basic requirements of school. Forty-four percent received past or current homebound tutoring. The multiple stressors of physical complaints, cognitive difficulties, and missed instruction create significant barriers for academic and social functioning.

The research design controlled for many variables that may impact/influence cognitive performance. Participants were matched on IQ, age, gender, and SES, and data were collected on physical health in the form of the BMI. No differences were found between groups. Data were collected on other variables that potentially could have had a significant impact on cognitive functioning, such as levels of depression and previous academic achievement. No differences were found, although the Lyme group did have increased physical complaints on the depression measure (such as chronic fatigue, sleep disturbance)—but not depressed mood, loss of pleasure in activities, or negative self-evaluations. Sleeplessness and fatigue were ruled out as potential mediating variables.

The findings of the present study are consistent with studies by Bloom et al. (1998) and Tager et al. (2001) but extend their work by having a larger sample size and controlling for more potential covariates, and the present study included a more comprehensive assessment of memory and executive functions. It differs from the study by Adams et al. (1994) in that the sample participants that they tested were treated for Lyme disease in its early stages (less than six months). This study improves on previous research by examining adolescents with a history of persistent symptoms, after treatment for Lyme disease, who were not preselected based on the reports of cognitive deficits; in addition, this study examined both subjective feelings of cognitive difficulty and objective measures of cognitive performance. It surveyed executive functioning within the context of other cognitive and memory abilities and examined the memory constructs of short-term memory, long-term recall, and recognition memory abilities together, while controlling for a participants' age, gender, overall IQ, and SES. Previous studies (Tager et al., 2001) have either required participants to experience persistent cognitive complaints, as an inclusion criteria for the study, or examined cognitive abilities of adolescents with Lyme disease who were identified early in the disease course and treated adequately (Adams et al., 1994, 1999). Most studies have utilized participants who came from a single geographic area and who were also being treated for Lyme disease by the same group of researchers conducting research. This study draws participants from a broad swath of the northeast of the United States. Most studies conducted did not have examiners that were blind to the study condition; in this study, a few of the Lyme participants and almost all of the comparison group participants were evaluated by blind examiners. Finally, no study has compared current academic functioning and school attendance, while controlling for predisease achievement by utilizing elementary school standardized test measures for reading and math between Lyme and non-Lyme groups (which this study does).

A limitation of this study was the inability to perform blood testing to confirm that the comparison group did not have Lyme disease. Because of the size of the comparison group and the fact that all of the parents denied that their children had a history of a tick bite, an EM rash, symptoms relating to a Lyme infection, or other chronic physical complaints, it is highly unlikely that a significant number of comparison group participants had been infected with an agent of Lyme disease. Referral bias is another possible study limitation, in that

adolescents with Lyme who were experiencing cognitive complaints may have been more interested in participating in this study than those who were not. A final limitation is the lack of heterogeneity across both groups in regards to SES and ethnicity; with both groups entirely Caucasian and mostly from a high SES background, whether outcomes for those from different SES and ethnic backgrounds would be different is unknown.

Directions for Future Research

The next logical step in the study of adolescents with Lyme disease would be to examine adolescents with subclinical Lyme disease, using materials and methods similar to those used in this study. A large controversy currently exists relating to the diagnosis of Lyme disease. The CDC criteria for blood tests include a Western Blot test that is positive on specific bands (2 of 3 bands: 24 kDa, 39 kDa, and 41 kDa; or 5 of 10 bands: 18 kDa, 21 kDa, 28 kDa, 30 kDa, 39 kDa, 41 kDa, 45 kDa, 58 kDa, 66 kDa, and 93 kDa). Some practitioners argue that CDC criteria are too narrow and that patients with similar symptoms but slightly different blood test results present themselves in similar ways, and they propose a more inclusive definition of a positive blood test for Lyme. About three-quarters of the potential applicants screened for this study did not meet CDC serologic criteria but carried a diagnosis of Lyme disease. A comparison of neuropsychological performance between this subclinical group and a group that meets CDC criteria would be helpful to determine functional differences.

This sample also represented middle- to upper-middle-class SES, educated, Caucasian, suburban participants, with access to educational and medical resources. It would be important to attempt to recreate this study in more rural communities, where the risk of Lyme is the same but there may be fewer resources for treatment.

A final area of research would be to follow up and reevaluate the study participants in five years. Few research studies have followed participants longitudinally. The ability to understand whether the cognitive profile and quality of life indicators of an adolescent with Lyme disease changes over time would provide critical information regarding long-term prognosis.

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