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# Neuropsychological Functioning in Chronic Lyme Disease

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Lyme disease is currently the most common vector-borne illness in the United States. The disease is multisystemic, and chronic disease, in particular, may be associated with neuropsychological deficits. However, to date, only a few empirical studies exist, which examine the neuropsychological sequelae associated with chronic Lyme disease. A review of the literature shows that the deficits observed in adults with chronic Lyme disease are generally consistent with the deficits that can be seen in processes with primarily frontal systems involvement. These observations are generally consistent with neuroradiologic findings. The clinical presentation in chronic Lyme disease and the nature of the neuropsychological deficits are discussed, as are several central issues in understanding neuropsychological functioning in chronic Lyme disease, such as the impact of chronic illness, response to treatment, and the relationship between neuropsychological performance and depression, fatigue, and neurological indicators of disease.

**KEY WORDS:** Lyme disease; neuroborreliosis; neuropsychological functioning; chronic illness; fatigue.

Lyme disease was first recognized as a cause of arthritis in 1975 (Steere et al., 1977), and it is now the most common vector-borne disease in the United States (White et al., 1991). Lyme disease is multisystemic, with dermatologic, arthritic, ophthalmologic, cardiac, neurologic, and psychiatric manifestations (Burgdorfer, 1991). The chronic phase of the illness may also be associated with neuropsychological deficits, though these are among the most poorly understood and poorly defined manifestations of Lyme disease. The initial sections of this review discuss the epidemiology, transmission, and clinical presentation of Lyme disease, including a brief overview of the psychiatric findings, differential diagnosis, pathogenesis, and EEG/neuroradiologic findings. These sections are followed by a review of the adult neuropsychological literature, with a detailed description of the published controlled studies and discussion highlighting some of the central issues in understanding neuropsychological functioning in chronic Lyme disease, such as the impact of chronic illness, the effects of medical treatment, and the relationship between neuropsychological functioning and depression, neurologic status, and fatigue. Given that neuropsychologically, Lyme disease may present differently in children than in adults, the effects of Lyme disease in children are not presented in this review; those interested in neuropsychological functioning in children can refer to the following papers: Adams et al., 1994, 1999; Bloom et al., 1998. Psychlit and Medline searches for the time period of January 1975 to April 2001 identified studies in the current review.

## EPIDEMIOLOGY

The identification of epidemic arthritis in Lyme, Connecticut, as a tick-borne illness was first made in the United States in 1975 (Steere et al., 1977), with the earliest documented case of Lyme disease in the United States occurring in 1962 (Steere et al., 1986). In Europe, however, a tick-borne disease much like Lyme disease, Garin–Bujadoux–Bannwarth's syndrome, has been recognized for over 100 years. In the United States, national surveillance of Lyme disease began in 1982, though national

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mandatory reporting has been in effect only since 1991 (Centers for Disease Control [CDC], 1991). In 1995, there were 11,700 reported cases of Lyme disease across 43 states, with foci in the Northeast from Massachusetts to Maryland (greatest in New York), the Midwest in Minnesota and Wisconsin, and the West in California and Oregon (CDC, 1995). At that time, the incidence was 4.49 per 100,000 (CDC, 1995), although in areas of focal epidemic, attack rates have been reported to reach up to 60%, as was found among residents living in the area surrounding a nature preserve in a coastal Massachusetts community (Lastavica et al., 1989).

Steere et al. (1986) examined the risk factors for infection in a study of 160 inhabitants of an endemic area, Great Island, Massachusetts. The male-to-female infection rate was found to be 1.2:1, with the rate of infection increasing with age (this is in contrast with a CDC report that found a peak at ages 25–44). Steere et al. found that affected and unaffected individuals did *not* differ significantly in terms of pet ownership or outdoor activity level. The risk of infection is seasonal, with peaks in the months of June and October, corresponding to the peak feeding times of ixodid ticks.

## TRANSMISSION

In 1982, the spirochete *Borrelia burgdorferi* was identified as the causative agent of Lyme disease (Burgdorfer et al., 1982). The spirochete is transmitted by the bite of an infected nymphal or adult female ixodes tick belonging to the *Ixodes ricinus* complex, including *I. dammini* (also called *I. scapularis*, which is also a vector for the agents of human granulocytic ehrlichiosis and babesiosis) in the Northeastern and Midwestern United States, *I. pacificus* in the Western United States, *I. ricinus* in Europe, and *I. persulcatus* in Asia (Steere, 1989). Ticks of this kind feed once during each of their three stages of their 2-year life cycle, with the larval ticks typically feeding during late summer; the nymphal ticks, during the following spring and early summer; and the adult ticks, during that autumn. The preferred host for both the larval and nymphal ticks is the white-footed mouse, which is tolerant to infection, with humans serving as incidental hosts. After a larval tick feeds on an infected host, the spirochetes remain within the midgut of the tick until the tick attaches itself to a new host the following year. The spirochetes then migrate to the tick's salivary glands and are injected into the new host when the tick feeds. Ticks must remain attached to the host for 12–48 hr for transmission to occur (Piesman, Mather, et al., 1987; Piesman, Maupin et al., 1987).

## PATHOGENESIS AND NEUROPATHOLOGICAL FINDINGS

The pathogenesis of this disease, particularly the persistent symptoms, is not yet fully understood. Steere (1997) hypothesized that following an incubation period of 3–32 days after the spirochete is injected into the skin or bloodstream of the host, the organism migrates outward in the skin, resulting in a characteristic skin lesion, or is blood-borne to organs such as the brain, liver, spleen, or to other skin sites. The organism has been shown to invade the central nervous system (CNS) within the first few weeks of infection (Garcia-Monco et al., 1990), and once in the CNS, the spirochetes may remain latent for extended periods of time, only to cause illness months to years after infection (Coyle, 1992). In later disease, the fate of the organism and cause of later symptoms is unclear (Steere et al., 1983). Coyle (1992) has proposed three possible mechanisms to explain later neurologic infection: (1) disease could result from persistent infection; (2) disease could result from a spirochete-triggered specific immune response; or (3) disease could result from a spirochete-triggered nonspecific inflammatory process. Coyle notes that support exists for all three mechanisms, and it is possible that different manifestations of the disease have different underlying processes. Rowe (2000) describes the possible mechanisms underlying chronic disease in similar terms, stating that persisting disease may result from continued presence of the spirochetes, or from the host immune response against the organism or against tissue autoantigens. Indeed, the possibility of a triggered autoimmune response in Lyme disease is being considered (e.g., Sigal and Williams, 1997), though this issue continues to be debated (Rowe, 2000).

Particularly, given that the disease tends not to be lethal and the causal agent was identified less than 20 years ago, neuropathological findings in neuroborreliosis have not been well described. Several case reports indicate hypoxic–ischemic damage caused by occlusive vascular changes, with perivascular leukocyte infiltration and meningitis (Miklossy et al., 1990; Oksi et al., 1993). In addition, Kobayashi et al. (1997) describe an autopsied case that showed only mild occlusive vascular changes, and more prominently, spongiform changes, neuronal cell loss, and microglial activation involving the cerebral cortex, thalamus, superior colliculus, dentate nucleus, inferior olivary nucleus, and spinal cord.

## CLINICAL PRESENTATION

Lyme disease has often been described as occurring in three stages: acute local, early/acute disseminated,

and late/chronic disseminated. The distinction of separate phases, however, is likely artificial, as the symptoms from each "stage" can overlap, and patients may remain asymptomatic during one or more stages. Currently, Lyme disease is more often categorized as simply either "acute" or "chronic," with the label of "chronic" disease generally referring to the persistence of symptoms despite standard antibiotic therapy. Nonetheless, for the purpose of illustrating the varying clinical presentations and typical course, the symptoms will be described in the traditionally identified phases.

### Acute Local

The most characteristic manifestation of early infection is the annular skin lesion, erythema chronicum migrans (now referred to as simply erythema migrans [EM]), which occurs in 60–80% of patients with Lyme disease (Coyle, 1992). The skin lesion is often described as a pathognomonic indicator of Lyme disease, though this has become one of many debated diagnostic issues (Melski, 1999). In addition to the rash, a flu-like illness is often present in the early stage of infection (Fallon and Nields, 1994; Pachner, 1986; Steere, 1989; Steere et al., 1984,1985). Flu-like symptoms tend to include headache, stiff neck, lethargy, irritability, fatigue, malaise, sore throat, fever, myalgias, arthralgias, chills, lymphadenopathy, or abdominal pain (Pachner, 1986; Pachner and Steere, 1985; Reik et al., 1986; Steere et al., 1983). In a focal epidemic in coastal Massachusetts, 91% of infected patients experienced the typical early symptoms of EM or flu-like illness (Lastavica et al., 1989). However, Steere et al. (1983) found that with the exception of fatigue and lethargy, which were often constant, the early signs and symptoms of Lyme disease are frequently intermittent and variable during a period of several weeks. Among a subset of patients, the symptoms associated with later phases of the disease may be the first manifestations of infection.

### Early/Acute Disseminated

In approximately 15–20% of patients, the disease disseminates to other organ systems (Pachner et al., 1989). Symptoms indicative of dissemination tend to develop approximately 1 month following initial infection and typically include neurologic abnormalities, or less likely, cardiac dysfunction (Pachner and Steere, 1985). In most cases, the symptoms resolve within months (Pachner et al., 1989).

The classic neurologic triad of symptoms at this stage includes meningitis, cranial neuritis, and radiculoneuritis, though these symptoms can occur alone or in any combination (Halperin, 1999; Pachner and Steere, 1985). In addition to the peripheral nervous system abnormalities, encephalitic symptoms consisting of sleep disturbances, difficulty concentrating, poor memory, irritability, and emotional lability may also be present (Pachner and Steere, 1985).

### Late/Chronic Disseminated

Chronic abnormalities consist primarily of arthritis, mild to severe persistent encephalitic/encephalopathic symptoms, polyneuropathy, and profound fatigue (Fallon et al., 1992). Polyneuropathies can include spinal or radicular pain, paresthesias, sensory loss, and lower motor neuron weakness (Fallon et al., 1992). Chronic neurologic abnormalities may emerge from 1 month up to 14 years after initial infection (Logigian et al., 1990).

Encephalitic symptoms may be particularly common in long-standing Lyme borreliosis (Halperin et al., 1989). These symptoms, which include the neuropsychological symptoms to be more fully defined in the following sections, typically involve complaints of difficulty with concentration and memory (Fallon et al., 1992; Halperin et al., 1989). Other common complaints include word-finding problems, sleep disturbances, photophobia, auditory hyperacusis, dyslexic-like errors when writing or speaking, spatial disorientation, extreme irritability, and mood lability (Fallon et al., 1992; Logigian et al., 1990). In this phase of the disease, intrathecal production of specific antibodies to *B. burgdorferi* may occur and is suggestive of active CNS disease (Halperin et al., 1989). However, these symptoms may also occur in patients with no cerebrospinal fluid (CSF) findings or other evidence of CNS invasion (Fallon et al., 1997). Often in this phase, the distinction is made between "chronic Lyme disease" (generally referring to persistent symptoms with serologic or intrathecal evidence of ongoing infection despite standard treatment), which may include Lyme neuroborreliosis (*neurologic* symptoms with objective evidence of CNS infection), and "post-Lyme syndrome" (persistent symptoms despite standard treatment *without* objective evidence of continued infection). However, it is not yet known if these are separate syndromes, and some authors use these terms interchangeably. Halperin (2000) suggests that when encephalopathy occurs in the absence of objective CNS dysfunction, patients typically have active inflammatory disease evident elsewhere. He speculates that Lyme encephalopathy is most likely a metabolic encephalopathy, possibly mediated by inflammatory cytokines.

### Atypical Neurologic Presentations

Although rare, case reports also indicate that late Lyme disease may be associated with dementia, which can be severe enough to require total care (Ackermann et al., 1988; MacDonald and Miranda, 1987; Reik et al., 1986), delirium (Caliendo et al., 1995), demyelinating disorders mimicking multiple sclerosis (MS; Oksi et al., 1996; Pachner et al., 1989; Reik et al., 1985), seizure disorders (Oksi et al., 1996; Reik et al., 1986), hemiparesis (Oksi et al., 1996; Uldry et al., 1987; Veenendaal-Hilbers et al., 1988), Tullio phenomenon (i.e., vertigo and nystagmus in response to loud sounds; Nields and Kveton, 1991), intracranial arteritis (Midgard and Hofstad, 1987), aphasia (Broderick et al., 1987; Kohler et al., 1988), apraxia (Broderick et al., 1987), ataxia (Ackermann et al., 1988; Kohler et al., 1988; Pachner et al., 1989; Weder et al., 1987), vasculitis (Oksi et al., 1996; Schmutzhard et al., 1988), recurrent transient ischemic attacks (Kohler et al., 1988), and strokes (Kohler et al., 1988; Uldry et al., 1987; Weder et al., 1987). It is not surprising that Lyme disease has been dubbed "the new great imitator" (Pachner, 1989), as its tremendous variability in symptom presentation is reminiscent of syphilis, another spirochetal disease. Others, however, have speculated that as we learn more about Lyme disease, we may discover that misdiagnosis accounts for what has been supposed to be the protean nature of the disease (Finkel and Halperin, 1992).

### Differential Diagnosis

The CDC's national surveillance case definition for Lyme disease includes the following diagnostic criteria: (1) EM of at least 5 cm in diameter or (2) laboratory confirmation of exposure to *B. burgdorferi* and at least one systemic manifestation. Systemic manifestation must be either be musculoskeletal (arthritis), neurologic (lymphocytic meningitis, cranial neuritis, radiculopathy, encephalomyelitis with intrathecal antibody production), or cardiac (second or third degree atrioventricular conduction delays). Laboratory confirmation requires the isolation of *B burgdorferi*, the demonstration of diagnostic level of *B. burgdorferi* immunoglobulin M or G (IgM or IgG) antibodies in serum or CSF, or a rising specific antibody titer on serum samples taken from acutely ill and convalescent patients (CDC, 1991).

Many clinicians and scientists feel that these criteria are too strict (Coyle, 1992; Fallon et al., 1992; Fallon and Nields, 1994). The limits and variability of serological tests (Bakken et al., 1992; Schwartz et al., 1989), the possibility of seronegative Lyme (Liegner, 1993), and the lack of matured antibody response in patients who are tested within the first few weeks of infection or who may not have received complete treatment early in the course of the disease (Halperin, 2000) create further diagnostic challenges. Appropriate epidemiologic data, including the presence of proper vectors and the spirochete in the environment, in-depth histories, complete physical examinations and diagnostic studies, and objective responses to therapy (Finkel and Halperin, 1992) may be helpful in diagnosis, particularly in ambiguous cases.

However, regardless of the diagnostic criteria used, diagnosis in some cases can be difficult, given the variety of symptom presentations. Consideration of differential diagnoses varies depending upon the phase and symptoms of the disease. Diagnostic uncertainty occurs most often in the disseminated phases of the disease, particularly when the symptoms of late Lyme disease are not preceded by the characteristic skin lesion (Pachner, 1989). The diseases with which it is most commonly confused are MS (Coyle, 1992; Fallon et al., 1992; Pachner and Steere, 1984; Steere, 1989), fibromyalgia (Fallon et al., 1992; Steere, 1989; Steere et al., 1993), and chronic fatigue syndrome (CFS; Fallon et al., 1992; Steere, 1989; Steere et al., 1993). Given that Lyme disease may involve the presence of oligoclonal bands in the CSF, hyperintense white matter lesions on T2-weighted images, and cross-reactivity between myelin basic protein and a borrelia protein, the ability to differentiate between Lyme disease and MS may be especially difficult in certain patients (Karussis et al., 1999). Some authors are also careful to note that the presence of CFS or fibromyalgia does not necessarily exclude the possibility that these symptoms (e.g., fatigue, myalgia, arthralgia, headache, sleep disturbance) are reflective of Lyme disease, particularly given the hypothesis that CFS and fibromyalgia may be triggered by infectious agents (Fallon et al., 1998). Depending on the presenting symptoms, other rule-out diagnoses can include rheumatoid arthritis (Fallon et al., 1992), Reiter's syndrome (Steere et al., 1984), late stage syphilis (Fallon et al., 1992; Pachner and Steere, 1984), Guillian–Barre syndrome (Fallon et al., 1992; Pachner and Steere, 1984), acquired immune deficiency syndrome (Fallon et al., 1992), systemic lupus (Fallon et al., 1992), amyotrophic lateral sclerosis (Steere, 1989), brain tumor (Pachner, 1989), other dementias (Pachner, 1989; Steere, 1989), and psychiatric illnesses (Fallon et al., 1992; Pachner, 1989).

### Depression and Other Psychiatric Findings

Psychiatric symptoms are most typically reported during the chronic phase of the illness, though these

symptoms are less frequently reported than are arthritis and encephalitis. With the exception of depression, psychiatric disturbances have been described primarily in case studies. The psychiatric disorders and symptoms described anecdotally in the literature include obsessive–compulsive disorder (Fallon et al., 1995; Fallon and Nields, 1994), panic (Fallon et al., 1993, 1995; Fallon and Nields, 1994), agoraphobia (Fallon and Nields, 1994), paranoia (Fallon et al., 1995), thought disorders (Roelcke et al., 1992), delusions (Fallon et al., 1995, Roelcke et al., 1992), hallucinations (Fallon et al., 1995; Fallon and Nields, 1994), anorexia nervosa (Pachner et al., 1989), violent outbursts (Fallon et al., 1995; Pachner et al., 1989), and mania (Fallon et al., 1993, 1995). In many of these cases, psychiatric symptoms reportedly occurred in patients with no prior histories of psychiatric disturbance and responded well to antibiotic therapy (Fallon and Nields, 1994).

Depression appears to be one of the most commonly reported and studied psychiatric problems in Lyme disease. Fallon and Nields (1994) reviewed nine studies that evaluated the incidence of depression among patients with Lyme disease. Problems with irritability, mood lability, or depression were reported in seven of the nine studies, with the frequency of these symptoms ranging from 26% to 66% of the samples. As was observed in many of the other cases mentioned above, Fallon and Nields found that depression was common among patients who had no prior history of a depressive episode.

Fallon et al. (1993) note that, as is true for other CNS disorders, it is difficult to determine whether the psychiatric symptoms, particularly depression, are direct neuropsychiatric consequences of CNS infection or occur secondary to another process. In support of the former theory, they report that improvement in psychiatric symptoms can be seen with antibiotic therapy, and the onset of psychiatric symptoms does not always coincide with worsening physical symptoms. Contrary to these observations, Finkel and Halperin (1992) report that antibiotic therapy has little effect on the depressive symptoms in patients with Lyme disease.

## EEG AND NEURORADIOLOGIC FINDINGS

Aside from positive CSF findings, other evidence for CNS infection comes from EEG and neuroimaging studies. EEG is often normal, except in cases of encephalitis. For example, Pachner and Steere (1985) found EEG abnormalities in 9 of 11 patients with encephalitis, but in only 4 of 27 Lyme patients without encephalitic symptoms (e.g., sleep disturbance, difficulty concentrating, poor memory, irritability, and mood lability). The EEG abnormalities tended to include mild slowing, often with excess sharp wave activity. Broderick et al. (1987) also described a Lyme patient with aphasia and apraxia, who showed persistent slow wave activity over the entire left hemisphere, that was maximal in the left central temporo-parietal region.

Neuroimaging studies are also often unremarkable, even in some patients with debilitating neurologic/neuropsychologic deficits (Coyle, 1992). When abnormalities on magnetic resonance imaging (MRI) are present, findings tend to include lesions in the periventricular white matter (Halperin et al., 1988, 1989; Kohler et al., 1988; Logigian et al., 1990; Pachner et al., 1989). In some cases, the lesions have been found to be reversible following antibiotic treatment (Halperin et al., 1989; Oksi et al., 1996). Other neuroimaging findings include enlarged ventricles (Kohler et al., 1988; Oksi et al., 1996), cortical atrophy (Caliendo et al., 1995; Finkel and Halperin, 1992; Oksi et al., 1996), and, more rarely, involvement of the basal ganglia (Finkel and Halperin, 1992). Single-photon-emission computed tomography (SPECT) is more likely to show abnormalities, which typically include multifocal areas of decreased perfusion in both the cortex and subcortical white matter (Fallon et al., 1997). In a review of several recent studies, Fallon et al. (1997) note that SPECT images tend to show a heterogeneous pattern that is somewhat nonspecific and may be similar to abnormalities seen in patients with Creutzfeldt–Jakob disease, cerebral vasculitis, and CFS.

Logigian et al. (1997) compared SPECT findings in 22 patients with Lyme disease (13 with Lyme encephalopathy, 9 with probable Lyme encephalopathy) to 26 healthy controls. They observed a multifocal pattern of cerebral hypoperfusion affecting both the cortex and deep structures of the brain in all 13 patients with objective evidence of Lyme encephalopathy. Perfusion defects were most prominent in the subcortical frontotemporal white matter and basal ganglia, as well as in the frontal cortex and cingulate gyrus. This pattern was also apparent in 5 of the 9 patients with probable Lyme encephalopathy (56%), as well as in 2 of 26 normal controls (15%). Perfusion defects in the Lyme encephalopathy group were greater than in the probable encephalopathy group, which in turn, were greater than in the control group. Similar to findings of reversible lesions on MRI following treatment (Halperin et al., 1989; Oksi et al., 1996), Logigian et al. (1997) found that after a 1-month course of intravenous antibiotic treatment, all 13 patients with Lyme encephalopathy showed improvement in cerebral perfusion on follow-up SPECT, with perfusion in these patients appearing similar to that of the probable encephalopathy group. Eleven of the

13 patients also reported subjective improvement in memory and other neuropsychiatric symptoms. Thus, perfusion defects appear to be a seemingly pervasive difficulty in Lyme encephalopathy that is at least partially reversible with antibiotic therapy.

The etiology of these defects, however, is not entirely clear. Fallon et al. (1997) state that hypoperfusion defects may result from any process that alters the radiotracer distribution, including vascular delivery to neurons, transport of the tracer into the cells, or retention of the radiotracer in the cells. Problems may, therefore, result from cellular dysfunction (e.g., due to direct infection of neurons), metabolic disturbance (e.g., indirect effects of neurotoxic immunomodulators), or vascular problems (e.g., vasculitis).

## NEUROPSYCHOLOGICAL FUNCTIONING

As stated in preceding sections, when present, neuropsychological dysfunction tends to occur along with other encephalitic symptoms in the chronic phase of the disease. As such, the relatively sparse literature on the neuropsychological sequelae of Lyme disease almost exclusively involves study of patients with late disseminated disease. It is unclear how often patients in this phase present with these symptoms. Ackermann et al. (1984) found that approximately 20% of those with neurological manifestations of the European tick-borne disease, Garin–Bujadoux–Bannwarth's syndrome, complain of difficulty with memory, concentration, or behavioral changes (Ackermann et al., 1984). Similarly, Shadick et al. (1994) found that 31% of randomly selected patients with prior histories of Lyme disease showed persistent neuropsychological impairment at a mean of 6 years after infection. The essential details of 11 controlled neuropsychological studies reported in the literature are outlined in Table 1 (presented in chronological order, as in the text). Omitted from this table and discussion is a study conducted by Shadick et al. (1999), given that the specifics of the neurocognitive examination were not included in their report.

### Review of Controlled Studies

The first controlled study of neuropsychological functioning in Lyme disease reported in the literature examined 15 Lyme patients with cognitive complaints, which persisted beyond antibiotic therapy (Krupp et al., 1991). Compared with 10 healthy controls, the Lyme group performed significantly worse on a measure of verbal fluency (Controlled Oral Word Association [COWA]) and several measures of memory (Wechsler Memory Scale-Revised [WMS-R] Logical Memory, WMS-R Verbal Paired Associates, and the Selective Reminding Test [SRT]). The Lyme group also had significantly higher scores on a measure of depression. However, the differences between groups on the neuropsychological measures remained significant after statistically controlling for depression, suggesting that depression did not solely account for these differences. Krupp et al. also compared the Lyme group's performance to normative data, identifying the frequency of mild (defined as three test scores falling at least one standard deviation [*SD*] below the normative mean), moderate (four test scores $\leq$1 *SD*), and severe (five or more test scores $\leq$1 *SD* or three or more test scores $\leq$2 *SD*) impairment. Of the 15 Lyme patients, 9 were described as "impaired" (1 mild, 6 moderate, 2 severe). Eight of the 15 Lyme patients also underwent neuroimaging via MRI. Two of these patients, both of whom were described as cognitively impaired, had scans that revealed one or more small areas of increased signal intensity in the subcortical white matter on T2-weighted images, though overall, Krupp et al. stated that MRI findings were not predictably related to neurocognitive findings. Similarly, antibody levels in serum and CSF (the latter presumably reflective of CNS infection) had no relationship to neuropsychological functioning. In contrast, fatigue severity was inversely correlated with memory performance. Depression was also significantly correlated with neuropsychological performance, though this relationship was not in the expected direction, in that greater depression was associated with better memory performance. However, in 5 of the 6 Lyme patients *without* cognitive dysfunction, the depression ratings were among the highest in the group, suggesting that in these patients, psychological factors likely contributed to their perception of neuropsychological dysfunction (one of the criteria for inclusion in the study).

Kaplan et al. (1992) examined the impact of psychological factors, particularly depression, anxiety, and somatic concerns, on memory functioning in 20 patients with Lyme encephalopathy (defined as complaints of disturbances in memory, mood, or sleep). Nineteen of the 20 patients had abnormalities on at least one neurological test, including 13 with abnormal CSF studies and 2 with abnormal MRI scans. In an attempt to control for the affective and physical symptoms of the disease, these patients were compared with 11 depressed patients with cognitive complaints determined to be due to depression and 11 patients with fibromyalgia. Kaplan et al. found that the Lyme patients performed significantly worse on the WMS Visual Reproduction and Associate Learning subtests, as well as on the recall trials of the California Verbal Learning Test (CVLT). Delayed recall on the CVLT, in particular, was sensitive in identifying group membership

**Table I.** Essential Details of the 11 Controlled Studies in the Literature

| Study | *N* | Lyme inclusion criteria | Neuropsychological tests | Behavioral measures |
|---|---|---|---|---|
| Krupp et al., 1991 | 15 patients with Lyme<br>10 healthy hospital personnel controls matched for age and education | 1. History of prior *B burgdorferi* infection based on physical findings (dermatologic, rheumatologic, or of peripheral nervous system) and positive serum antibody titers to *B burgdorferi*<br>2. Complaints of persistent cognitive dysfunction that followed clinical signs of Lyme borreliosis and did not respond to initial antibiotic treatment<br>3. History of normal neurobehavioral functioning before the onset of Lyme borreliosis | *Premorbid IQ*<br>WAIS-R<br>Information<br>Vocabulary<br>*Attention/Information Processing*<br>WAIS-R<br>Digit Span<br>Digit Symbol<br>Trail Making Test<br>Part A<br>*Executive Functioning*<br>Trail Making Test<br>Part B<br>WAIS-R<br>Similarities<br>COWA*<br>Booklet Category Test<br>*Visuospatial Skills*<br>WAIS-R<br>Block Design<br>Object Assembly<br>*Memory*<br>Selective Reminding Test, 6 trials<br>Total recall*<br>long-term retrieval*<br>long-term storage*<br>delayed recall*<br>consistent retrieval*<br>recognition<br>WMS-R<br>Logical Memory, immediate recall*<br>Paired Associates* | CES-D*<br>Fatigue Severity Scale (NR) |
| Kaplan et al., 1992 | 20 patients with Lyme (L), a subset of patients from Logigian, et al. 1990 study<br>11 control patients with depression (D)<br>11 control patients with fibromyalgia (F)<br>(C): Combined controls | 1. Disturbances in memory, mood, or sleep<br>2. Well recognized manifestations of Lyme | *Premorbid IQ*<br>WAIS-R or Shipley<br>*Attention/Information Processing*<br>WMS<br>Digits forward<br>Digits backward<br>*Memory*<br>CVLT<br>Trial 5* (L < F,D)<br>Immediate recall* (L < C)<br>Delayed recall* (L < F)<br>Recognition<br>WMS<br>Logical Memory<br>Visual Reproductions* (L < C)<br>Associate Learning* (L < D)<br>Rey–Osterrieth Figure<br>Immediate recall<br>Delayed recall | Beck Depression Inventory<br>MMPI<br>Hypochondriasis* (F > L,D)<br>Depression* (D > L)<br>Hysteria* (F > L)<br>Psychopathic Deviate* (F,D > L)<br>Masculinity/Femininity<br>Paranoia* (D > L)<br>Psychasthenia* (D > L)<br>Schizophrenia* (D > L)<br>Hypomania<br>Social Introversion |

**Table II.** (*Continued*)

| Study | *N* | Lyme inclusion criteria | Neuropsychological tests | Behavioral measures |
|---|---|---|---|---|
| Shadick et al., 1994 | 38 patients with Lyme<br>43 healthy controls | Met CDC criteria | *Premorbid IQ*<br>Shipley Abstraction<br>*Attention/Information Processing:*<br>Trail Making Test<br>Part A<br>*Executive Functioning*<br>Trail Making Test<br>Part B<br>Stroop interference<br>*Motor Skills:*<br>Perdue Pegboard<br>Dominant hand*<br>Nondominant hand<br>*Memory*<br>CVLT<br>Trial 5<br>Short delay recall<br>Long delay recall*<br>WMS<br>Paired Associates<br>Visual Reproductions | None |
| Benke et al., 1995 | 20 patients with Lyme<br>20 non-brain damaged neurological patient controls matched for age and education | 1. Classical triad of meningitis, cranial neuritis, and radiculoneuritis<br>2. Intrathecal production of IgG of IgM antibodies during the acute phase of the disease | *Attention/Information Processing*<br>Letter cancellation task<br>Choice reaction time<br>Reaction time<br>Accuracy*<br>*Executive Functioning*<br>Mental flexibility test<br>Reaction time<br>Accuracy*<br>COWA*<br>Ravens Progressive Matrices<br>*Language*<br>Rapid Syllable Repetition*<br>*Visuospatial Skills*<br>WAIS<br>Block Design<br>*Memory*<br>German CVLT (MGT)<br>Trials 1–5*<br>Short delay free recall*<br>Short delay cued recall*<br>Long delay free recall*<br>Long delay cued recall*<br>Recognition* | None |

**Table II.** (*Continued*)

| Study | *N* | Lyme inclusion criteria | Neuropsychological tests | Behavioral measures |
|---|---|---|---|---|
| Bujak et al., 1996 | 23 patients with post-Lyme syndrome<br>23 patients fully recovered from Lyme | 1. Met CDC criteria<br>2. Completed full course of antibiotic therapy | *Attention/Information Processing*<br>WMS-R<br>Attention/concentration Index*<br>Trail Making Test<br>Part A<br>***Executive Functioning***<br>Part B<br>*Memory*<br>CVLT<br>WMS-R<br>Verbal Memory Index<br>Visual Memory Index<br>General Memory Index | Beck Depression Inventory*<br>MMPI<br>Hypochondriasis*<br>Depression<br>Hysteria*<br>Psychopathic Deviate<br>Masculinity/Femininity<br>Paranoia<br>Psychasthenia<br>Schizophrenia<br>Hypomania<br>Social Introversion<br>SCL–90-R<br>Somatization*<br>Obsessive*<br>Interpersonal sensitivity<br>Depression*<br>Anxiety*<br>Hostility*<br>Phobic anxiety<br>Paranoid ideation<br>Psychotic<br>General Severity*<br>Positive Symptom Distress<br>Positive Symptoms (total)* |
| Ravdin et al., 1996 | 21 patients with Lyme (L)<br>21 patients with osteomyelitis (O)<br>21 healthy controls (HC) | Met CDC criteria | *Premorbid IQ*<br>National Adult Reading Test<br>*Memory*<br>CVLT<br>Trials 1–5<br>Long delay free recall* (HC > L,O)<br>Discriminability<br>Serial position<br>Clustering strategy | Beck Depression Inventory<br>Cognitive Index<br>Fatigue Severity Scale* (L > O > HC)<br>Self-Rating Scale of Memory Functions* (L > O, HC) |
| Gaudino et al., 1997 | 38 patients with post-Lyme syndrome (PLS)<br>25 patient with chronic fatigue syndrome (CFS)<br>56 healthy controls (C) | 1. Met CDC criteria or had histories highly suggestive of Lyme disease<br>2. Seropositivity to *B burgdorferi* | | |

**Table II.** (*Continued*)

| Study | *N* | Lyme inclusion criteria | Neuropsychological tests | Behavioral measures |
|---|---|---|---|---|
| | | 3. Persistent severe fatigue for 6 or more months following antibiotic therapy | *Premorbid IQ*<br>WAIS-R<br>Information<br>Vocabulary<br>*Attention/Information Processing*<br>WAIS-R<br>Digit Symbol* (CFS < C)<br>Digit Span* (L < C)<br>*Executive Functioning*<br>Trail Making Test<br>Part B* (L < C)<br>COWA* (L < C)<br>*Motor Skills*<br>Finger Tapping Test<br>dominant hand* (L < C)<br>*Memory*<br>Selective Reminding Test<br>sum of recall* (L < C)<br>WMS-R<br>Logical Memory<br>Benton Visual Retention Test | CES-D* (L, CFS > C)<br>SCID<br>Fatigue Severity Scale* (L, CFS > C) |
| Pollina, Sliwinski et al., 1999 | 16 patients with histories of Lyme disease<br>15 healthy age and education matched controls | 1. Met CDC criteria<br>2. Persistent symptoms of fatigue or cognitive complaints despite adequate antibiotic therapy | *Premorbid IQ*<br>Shipley Vocabulary Test<br>*Attention/Information Processing*<br>Computerized RT Tasks<br>Matching (motor speed)<br>Alphabet–Arithmetic (cognitive speed)*<br>*Memory*<br>Selective Reminding Test<br>Long-term Storage<br>Consistent long-term retrieval*<br>Delayed recall* | CES-D*<br>Fatigue Severity Scale (NR) |
| Pollina, Elkins et al., 1999 | 25 patients with Lyme disease<br>23 community age- and education-matched controls (compared only on the computerized RT tasks) | 1. History of infection based on objective findings of EM rash, migratory arthritis, cranial neuropathy, and positive serum antibody titers for *B burgdorferi*<br>2. Persistence of fatigue or cognitive problems that did not resolve with antibiotic therapy at least 2 months before study | *Premorbid IQ*<br>Shipley Vocabulary<br>*Attention/Information Processing*<br>Computerized RT Tasks<br>Matching (motor speed)<br>Alphabet Arithmetic (cognitive speed)*<br>*Memory*<br>Selective Reminding Test | CES-D* |

**Table II.** (*Continued*)

| Study | *N* | Lyme inclusion criteria | Neuropsychological tests | Behavioral measures |
|---|---|---|---|---|
| Svetina et al., 1999 | 44 Lyme patients<br>43 Healthy controls | 1. Exposure to endemic area<br>2. Constellation of signs and symptoms of Lyme disease<br>3. Positive ELISA with confirmation by Western blot<br>4. PCR | *Executive Functioning*<br>COWA<br>*Language*<br>Boston Naming Test*<br>*Memory*<br>CVLT (long delay free recall) | Beck Depression Inventory |
| Kaplan et al., 1999 | 14 Lyme Encephalopathy patients<br>18 post-Lyme patients<br>15 age- and education-matched controls | 1. Met CDC criteria<br>2. Encephalopathy group had intrathecal antibody production to *B. burgdorferi*, elevated protein, or positive PCR.<br>3. Post-Lyme group had normal CSF studies | *Premorbid IQ*<br>Shipley<br>*Attention/Information Processing*<br>WAIS-R<br>Digit Span<br>Digit Symbol<br>Gordon Diagnostic System<br>Simple RT<br>Choice RT*<br>2 and 7 Test<br>Automatic<br>Controlled*<br>Trail Making Test<br>Part A<br>*Executive Functioning*<br>Trail Making Test<br>Part B<br>COWA<br>*Motor Skills*<br>Finger Tapping Test<br>*Visuo-Spatial Skills*<br>Hooper VOT<br>Rey–Osterrieth Figure copy<br>*Language*<br>Boston Naming Test<br>*Memory*<br>Selective Reminding Test<br>Long-term storage*<br>Consistent long-term retrieval*<br>Recognition*<br>Delayed recall<br>Rey–Osterrieth figure<br>Immediate recall<br>Delayed recall | Beck Depression Inventory*<br>State Trait Anxiety Inventory<br>State*<br>Trait |

*Note.* CES-D: Centers for Epidemiologic Studies Depression Scale; COWA: Controlled Oral Word Association; CVLT: California Verbal Learning Test; MMPI: Minnesota Multiphasic Personality Inventory; SCID: Structured Clinical Interview of the *Diagnostic and Statistical Manual of Mental Disorders*; SCL–90-R: Symptom Checklist90—Revised; WAIS-(R): Wechsler Adult Intelligence Scale (Revised); WMS (R): Wechsler Memory Scale-(Revised).
*$p < .05$.

in a discriminant function analysis. Psychopathology was also measured using the Minnesota Multiphasic Personality Inventory (MMPI) and the Beck Depression Inventory (BDI). On the MMPI, the Lyme group had lower scores on the scales most sensitive to depression and anxiety relative to the depressed group, and fewer somatic concerns than the fibromyalgia group. In contrast with MMPI findings, there was no significant difference among groups on the BDI. Depression, as measured by the MMPI, had a significant negative correlation only with the Associate Learning subtest of the WMS in the Lyme group, and not with any of the other memory measures. When the Lyme group was divided in two groups based on their MMPI scale 1 (Hypochondriasis) score, there was no difference in memory performance between the high- and low-scoring groups. When divided based on the MMPI scale 2 (Depression) score, only immediate recall on the CVLT yielded significant differences between groups (with the group with greater depression showing worse memory performance). Thus, Kaplan et al. concluded that the memory impairment observed in Lyme encephalopathy cannot be explained solely by affective symptoms, despite the common finding that Lyme patients endorse more depressive symptoms than do normal controls.

Shadick et al. (1994) examined the prevalence of persistent symptoms in 38 randomly selected patients from the community with histories of Lyme disease. Compared with 43 healthy controls, overall, the Lyme group performed significantly poorer on the delayed recall trial of the CVLT, as well as on the Purdue Pegboard (dominant hand), a measure of fine motor coordination. Twelve of the 38 patients with Lyme disease scored more than two standard deviations below the mean on two or more memory tests, whereas only 5 of the 43 control participants showed such poor performances. For unclear reasons, however, only 4 of the Lyme patients were described as showing "neurocognitive sequelae." Two of those patients were diagnosed with mild encephalopathy, 1 with neuroborreliosis, and 1 with progressive supranuclear palsy. The latter two participants had positive Lyme titers. The only significant risk factor for persistent neurocognitive impairment was the length of infection before treatment. Unfortunately, although the authors also measured the prevalence of a number of physical sequelae, as well as serum antibody reactivity, they did not examine the relationship between these variables and neurocognitive functioning in the group as a whole.

A European study compared cognitive functioning in 20 patients with long-standing Lyme disease (mean of 52 months post acute infection) to 20 non-brain-damaged neurologic controls (Benke et al., 1995). Nineteen of the 20 participants with Lyme disease showed CSF evidence of lymphocytic pleocytosis during acute illness. Results of neuropsychological testing showed that the Lyme group performed significantly worse on both the recall and recognition indices of the German CVLT, verbal fluency, rapid syllable repetition, and the accuracy scores of mental flexibility and choice reaction time tasks. Memory was frequently affected, with 50% of the patients in the Lyme group performing at or below an unspecified cutoff score based on the control group's performance. Among these patients, 6 showed only memory deficits, whereas the remaining 4 demonstrated global neuropsychological impairment. The severity of neurological deficits at the onset of the illness was significantly correlated with performance on only the mental flexibility task, suggesting that the degree of neurological impairment was not a good indicator of overall neuropsychological performance. Length of time, since the diagnosis was made, was not correlated with any of the neuropsychological variables. Overall, Benke et al. state that this study demonstrates that cognitive deficits may persist in Lyme disease for years, even in patients with only minor residual neurological symptoms.

Bujak et al. (1996) compared neuropsychological and psychological functioning in 23 patients with "post-Lyme syndrome" (defined as persistent arthralgia, fatigue, and subjective memory loss despite presumably adequate antibiotic therapy) to 23 patients who had prior histories of Lyme disease but no residual symptoms. All patients showed antibody reactivity during the initial phase of the disease, and at the time of the current examination, 48% of *both* groups continued to be seropositive by immunoblotting or ELISA. Two of the post-Lyme patients additionally showed persistent neurologic involvement (Bell's palsy). Results of the neuropsychological evaluation revealed that both groups had poorer verbal than visual memory, though the post-Lyme group performed significantly worse than the recovered group on only the attention/concentration subscale of the WMS-R. The post-Lyme group also obtained higher scores on the somatization, obsessive–compulsive disorder, depression, anxiety, hostility, and summary scales of the Symptom Checklist-90-Revised (SCL-90-R), though all scores were within normal limits. In addition, higher scores were obtained in the post-Lyme group on the BDI, as well as scales 1 (Hypochondriasis) and 3 (Hysteria) of the MMPI, though, again, these scores were within the normal range. There was no correlation between fatigue or arthralgia (as measured by a visual analog scale) and performance on the WMS-R, BDI, and MMPI, nor was there any significant relationship between the BDI and WMS-R scores. The presence of both fatigue and arthralgia during the initial presentation of the disease was the best predictor of

subsequent development of post-Lyme syndrome (30% of the post-Lyme group met criteria for fibromyalgia, 13% for chronic fatigue, and 44% had symptoms resembling these conditions but failed to meet criteria). The presence of fatigue during *initial* illness increased the likelihood of post-Lyme syndrome by nearly 50-fold, and the presence of arthralgia by nearly 32-fold. Used together, this combination of symptoms correctly identified 21 and 23 patients in the post-Lyme and recovered groups, respectively. The authors concluded that patients with post-Lyme syndrome differ from those who have recovered from the illness on a number of clinical features, though the objective neuropsychological deficits were fairly limited. Because many of the patients with persistent symptoms had undergone multiple courses of antibiotic therapy without prolonged benefit in their chronic symptoms, Bujak et al. state that *active* borrelial infection in the brain is an unlikely cause of post-Lyme syndrome. Rather, they consider the possibility that these patients had disseminated borreliosis with subclinical CNS involvement during their Lyme disease infection, with this CNS disruption resulting in localized brain dysfunction and subsequent residual difficulties (i.e., subjective memory loss and poor concentration). They note that the specific factors (e.g., genetic or personality variables) that predispose patients to post-Lyme syndrome, however, remain undefined.

Ravdin et al. (1996) examined memory functioning in 21 patients with Lyme disease compared with both a patient control group consisting of 21 individuals with osteomyelitis and 21 healthy controls. The purpose of the study was to determine the extent to which memory dysfunction was present above and beyond what may be found in other patient groups as a result of systemic illness and coexisting emotional and physical complaints. They also examined the relationship between *self-report* of memory dysfunction and *objective* memory impairment, the latter measured by CVLT performance. Fifteen of the 21 patients in the Lyme group had neurologic complaints, though none had CSF evidence of Lyme disease, and polymerase chain reaction (PCR) was negative in all patients. Sixteen of the Lyme patients also had MRI data, with 3 of these patients showing "abnormal" scans (multifocal bright signals). Results of this study showed no significant differences among groups on a measure of the nonphysiologic aspects of depression (the BDI minus items measuring physical symptoms of depression). In contrast, both patient groups were significantly more fatigued than the healthy control group, with the Lyme patients describing greater fatigue than the osteomyelitis group. Similar to findings from previous studies, fatigue was significantly but inversely correlated with memory performance in the Lyme group. When controlling for the effects of fatigue, measures of memory functioning revealed significant differences between the healthy controls and both patient groups on recall indices. There was no significant difference between the Lyme and osteomyelitis groups, though closer analysis revealed that 38–48% of the patients in the Lyme group performed at the borderline to impaired level on total learning and long delay free recall (defined as *T* scores <40), whereas only 19–24% of the patients with osteomyelitis performed at or below this level. In contrast with performance on recall indices, there was no significant difference on the recognition trial, suggesting that the poorer performance in the patient groups was due primarily to retrieval deficits. The Lyme group was more likely to endorse memory dysfunction on a self-report measure than the other two groups, though there was no significant relationship between subjective ratings of daily memory capabilities and objective memory performance. *Subjective* ratings of memory impairment, however, were significantly correlated with both depression ratings and fatigue in the Lyme group.

Gaudino et al. (1997) further examined the relationship between physical and psychiatric symptomatology and cognitive complaints by comparing neuropsychological performance in 38 patient with post-Lyme syndrome (defined as severe fatigue, malaise, and cognitive complaints that persist 6 months or more after completion of adequate antibiotic therapy) to 25 patients with CFS and 56 healthy controls. Post-Lyme syndrome and CFS share a number of symptoms, including, most obviously, profound and debilitating fatigue, as well as a number of affective symptoms. Both illnesses, however, are heterogeneous with respect to the nature and severity of the clinical symptoms, as well as the presence of neuropsychiatric disturbance. Results showed that both CFS and post-Lyme patients described more fatigue and depression than did the healthy controls, though the two patient groups did not differ from each other on these measures. The relationship between depression and fatigue and the neuropsychological variables was not examined. On neuropsychological measures, the CFS group performed more poorly than did controls on only the Digit Symbol subtest of the Wechsler Adult Intelligence Scale-Revised (WAIS-R). In contrast, the Lyme group performed worse than the control group on measures of attention (Digit Span subtest of the WAIS-R), verbal learning (SRT), verbal fluency (COWA), and fine motor speed (Finger Tapping Test [FTT], dominant hand). When patients were further subgrouped according to premorbid psychiatric histories, Gaudino et al. found that post-Lyme patients with no premorbid psychiatric histories performed significantly worse than those with prior psychiatric histories on most cognitive tests, though these differences were statistically significant only on the

SRT and Digit Span subtest of the WAIS-R. Given that 9 of the 10 post-Lyme patients with premorbid psychiatric histories also had psychiatric disorders at the time of testing (whereas none of the patients without premorbid psychiatric histories had concurrent psychiatric disorders), the authors concluded that psychological factors may have contributed to the perception of cognitive loss in the patients with psychiatric disturbances. In contrast, among those patients who lacked histories of psychiatric difficulties, their subjective impressions of loss were confirmed on objective testing. In these instances, the objective neuropsychological deficits were attributed to a mild encephalopathic process resulting from Lyme disease.

Pollina, Sliwinski, et al. (1999) examined cognitive processing speed on a measure with minimal peripheral nerve/muscle functioning demands in a group of 16 patients (with histories of well-documented Lyme disease) who had completed standard antibiotic treatment at least 2 months before evaluation. Twelve of the 16 Lyme patients had CSF data available: 3 had intrathecal antibody synthesis, 2 had mildly elevated CSF protein, and none showed pleocytosis. In addition, "several" patients underwent MRI imaging, with nonspecific white matter lesions observed "occasionally." Compared with 15 age- and education-matched healthy control participants, the Lyme patients performed significantly poorer on a computerized measure of cognitive processing speed (Alphabet–Arithmetic task), though the groups did not differ on a simple perceptual/motor speed-matching task. Closer analysis of these findings suggested that the deficit on the speeded processing task was most likely due to slowness in initiating the cognitive processes involved in the task rather than repetitively performing the task. Performance on the measure of cognitive speed did not correlate with memory performance on the SRT (also poorer in the Lyme group), suggesting that these deficits were independent of one another. The Lyme group also reported significantly more depressive symptoms than did the healthy controls, though when depression was added to the analyses as a covariate, differences on the cognitive measures remained. In addition, fatigue was related to only one of the SRT variables, suggesting that noncognitive variables such as fatigue and depression did not have a significant impact on neuropsychological performance.

Pollina, Elkins, et al. (1999) extended their previous work suggesting that cognitive slowing is process-specific in Lyme patients by examining 25 patients with well-recognized manifestations of Lyme disease which, despite treatment, were followed by unresolved symptoms of fatigue and/or cognitive problems. Twenty-three community age- and education-matched volunteers were also examined. All participants underwent examination with the computerized measure of processing speed mentioned previously (Alphabet Arithmetic). The Lyme patients were also administered standard neuropsychological tests (e.g., measures of word-reading, fund of knowledge, expressive vocabulary, attentional capacity, psychomotor speed, speed of information processing, visuoconstruction, learning/memory, and depression). Age, level of depression, and estimated premorbid intellectual ability were used as covariates. Pollina and colleagues found that the groups did not differ on the experimental task in terms of accuracy, nor did they differ in terms of perceptual motor speed and incrementing speed. However, the Lyme patients showed slower speed of initiation relative to the healthy controls. In the Lyme patients, the authors found no relationship between initiation speed and performance on specific cognitive domains (test scores were combined to create domains of premorbid IQ, short-term memory, and long-term memory). Initiation speed was found to correlate with performance on part A of the Trail Making Test (TMT) and Digit Symbol, but not with part B of the TMT or the Paced Auditory Serial Addition Task (PASAT). The authors note that the Lyme patients reported more depressive symptoms than did the controls, though there was no significant correlation between their depression scores and initiation speed. In conclusion, Pollina, Elkins, et al. (1999) state that this study supports their hypothesis that Lyme patients experience cognitive slowing that is independent of age, premorbid abilities, and degree of depression, and that may be specific to the amount and type of information processing required by a given task. Their finding that initiation speed did not correlate with other cognitive domains argues against a pattern of global impairment, though the Lyme patients' performances were not compared with control data on the standard neuropsychological measures.

Svetina et al. (1999) examined confrontation naming in a group of 44 patients with confirmed Lyme disease and 43 healthy, serologic-negative controls. Ninety-one percent of the Lyme patients were vaguely described as having progressed to the "second stage." Svetina et al. note that word-finding difficulty is a frequent complaint of many patients with Lyme disease, though this aspect of language had not been examined previously. Svetina et al. also measured phonemic and semantic verbal fluency, memory, and depression. In their sample, 55% of the patients with Lyme disease complained of word-finding difficulties, in contrast with 14% of the controls. Results of formal testing revealed significantly lower Boston Naming Test (BNT) scores in the Lyme group relative to controls, though they found no difference between groups on the verbal fluency measures or on the other measures given. When the BNT scores were categorized according to

impairment (defined as a score of less than 2 *SD* below the mean of the control group; i.e., a cutoff of 51), 36% of the Lyme patients fell within this range, compared with only 9% of the control participants. There was no association between actual test performance on the BNT and self-report of naming difficulties. A significant correlation between naming and scores on the CVLT was found, suggesting a relationship between naming and memory retrieval; there was no significant correlation between the BNT and verbal fluency. When the groups were separated based on level of depression, there were no significant differences among groups on the BNT. In sum, the authors conclude that there appears to be a subtle naming deficit in Lyme disease that may be a result of a generalized impairment in retrieval, though in this group there was no significant difference in memory performance between the Lyme disease and control groups.

Lastly, Kaplan et al. (1999) investigated the relationship between objective evidence of CNS infection and neuropsychological performance. The study groups consisted of 32 patients who met CDC criteria for Lyme disease, including 14 patients with evidence of CNS infection (i.e., one or more signs of abnormal CSF: intrathecal antibody production to *B. burgdorferi*, elevated protein, or a positive PCR for *B. burgdorferi* DNA; "Lyme encephalopathy" group) and 18 patients without evidence of CNS infection ("post-Lyme" group). Fifteen age- and education-matched community and hospital volunteers without histories of Lyme disease were also studied. Most of the Lyme patients (11 of 14 Lyme encephalopathy patients and 13 of 18 post-Lyme patients) complained of memory problems, though none of the controls reported similar concerns. Results showed that the post-Lyme group had slower reaction times on the Gordon Diagnostic System (GDS), a vigilance task, than those of the control group (there was no significant difference between the other groups), and there was a nonsignificant trend in the post-Lyme group toward difficulty with selective attention. The Lyme encephalopathy group performed significantly worse in aspects of verbal learning (SRT) than the other two groups, which did not differ. On mood measures, both Lyme groups had higher depression scores than did the control group, with the post-Lyme patients reporting more depressive and state anxiety symptoms than did the Lyme encephalopathy or control group. Examination of the relationship between mood measures and neuropsychological performance revealed that higher levels of state anxiety were associated with poorer performance on the selective attention task in the whole sample and in the control group. In the post-Lyme group, higher state anxiety scores were also associated with slower reaction time on the GDS, but not with any other measure. The depression measure (BDI) did not correlate with neuropsychological performance on any of the attention or memory measures in any of the groups. Kaplan et al. make note of the finding that the post-Lyme group performed worse than did the other groups on measures of attention and psychomotor speed, and that anxiety was correlated with slower reaction time on the vigilance task. They speculate that anxiety may have affected performance in this group by narrowing the focus of attention beyond an adaptive level. Kaplan et al. state that, in contrast, the Lyme encephalopathy group appears to have a neurologic basis associated with their deficit (i.e., memory loss).

## DISCUSSION OF THE NEUROPSYCHOLOGICAL LITERATURE

### Summary of Cognitive Findings

Overall, the results of the neuropsychological studies in Lyme disease rather consistently demonstrate deficits on memory measures, with most difficulty with free recall on list-learning tasks (Benke et al., 1995; Gaudino et al., 1997; Kaplan et al., 1992, 1999; Krupp et al., 1991; Pollina, Sliwinski, et al., 1999; Ravdin et al., 1996; Shadick et al., 1994). Exceptions include the studies by Bujak et al. (1996) and Svetina et al. (1999). The lack of significant findings on the CVLT in the Svetina et al. study is somewhat surprising. The Bujak et al. study, however, did not utilize a healthy control group; rather, they compared patients with post-Lyme syndrome to patients who had apparently fully recovered from Lyme disease. The possibility that subtle deficits were present in "recovered" Lyme patients should be considered, however, particularly given that at the time of evaluation, 48% of *both* groups continued to be seropositive (of note, seropositivity is an indicator of past or present infection and not necessarily active disease). It is also possible that the discrepant findings reflect differences in the measures used, rather than the participants studied. Bujak et al. used the WMS-R, whereas the majority of the other studies report deficits on the CVLT or SRT, both verbal list-learning tasks. In other studies using subtests of the WMS-R such as Logical Memory (often in addition to the CVLT or SRT), findings have been more inconsistent, perhaps reflecting the greater demand for the use of active organization/mnemonic strategies and the requirements of sustained effort on the list-learning tasks (Kaplan and Jones-Woodward, 1997). In addition, Tremont et al. (2000) have found that verbal list-learning tasks such as the CVLT have a stronger relationship with measures of executive functioning than do other

verbal memory tasks (such as story recall). This finding is supported by functional imaging studies that have shown that tasks requiring active encoding and retrieval strategies involve substantial frontal systems activation (Fletcher et al., 1995; Grasby et al., 1993), whereas story recall tasks ("consolidation tasks") may be more purely reliant on the integrity of the hippocampus and other mesial temporal structures (Tremont et al., 2000). Thus, it is possible that the observed deficits on verbal list-learning tasks in chronic Lyme patients may reflect the additional impact of frontal systems dysfunction on learning and memory on these tasks. Consistent with this hypothesis (and in contrast with the impairments observed in performance on recall indices of verbal list-learning tasks), recognition performance in the Lyme groups has generally been found to be equivalent to that of the controls. A brief report by Masur et al. (1992) describes similar findings.

Often, deficits have also been found on the COWA (Benke et al., 1995; Gaudino et al., 1997; Krupp et al., 1991), a word-list generation task often described as a measure of verbal fluency and an indicator of frontal systems functioning, though this is not an entirely consistent finding (cf. Kaplan et al., 1999; Svetina et al., 1999). Other traditional "executive" tasks requiring set shifting, abstraction, concept formation, and response inhibition (e.g., part B of the TMT, Booklet Category Test, WAIS-R Similarities, Raven's Progressive Matrices, Stroop), however, have generally failed to distinguish patients with Lyme disease from controls, though other areas of functioning often considered as involving the frontal systems have shown impairment. These include deficits in mental flexibility (Benke et al., 1995), choice reaction time (Kaplan et al., 1999), selective attention (Kaplan et al., 1999), upper extremity fine motor dexterity (Gaudino et al., 1997; Shadick et al., 1994), and speed of information processing/initiation (Pollina, Elkins, et al., 1999; Pollina, Sliwinski, et al. 1999). Interestingly, Pollina, Sliwinski, et al. (1999) noted that the speed of information processing deficits observed in their group of chronic Lyme patients was not significantly related to performance on the SRT, suggesting that slowed processing cannot account for the deficits seen on this learning task. Language and oral/motor deficits have also been described, including impairments in rapid syllable repetition (Benke et al., 1995; Gasse et al., 1992), and, in one of two studies measuring the construct, confrontation naming (Svetina et al., 1999). Measures of brief attention (Benke et al., 1995; Bujak et al., 1996; Gaudino et al., 1997; Kaplan et al., 1992, 1999; Krupp et al., 1991) show more inconsistent results, though to some extent, the apparent inconsistencies may reflect differences in the measures used. Lastly, performance by the groups with Lyme disease on measures of general intelligence (Benke et al., 1995; Kaplan et al., 1992; Krupp et al., 1991; Ravdin et al., 1996) has consistently been comparable to that of the control groups.

Thus, the neuropsychological deficits observed in Lyme disease appear to predominantly reflect frontal systems dysfunction. These findings are consistent with positive results from neuroimaging studies in Lyme disease, though it should be noted that this appears to be a typical pattern of performance in Lyme disease regardless of whether imaging shows abnormalities. The nature of the deficits is, therefore, similar in many respects to the kind of deficits seen in other infectious disease processes involving primarily subcortical/frontal systems functioning such as HIV infection, as well as in autoimmune disorders and fatiguing illnesses involving subcortical white matter (e.g., MS, systemic lupus). The autoimmune disorders, in particular, may provide good conceptual models for Lyme disease, given the high overlap in physical, psychiatric, and neuropsychologic symptoms.

### Limitations of the Neuropsychological Literature

There are several limitations of the current literature that merit elaboration. First, the expected degree of cognitive impairment in Lyme disease is difficult to predict from the current literature. Most studies describe relatively mild deficits, though reliance on group statistics may obscure individual findings within a relatively heterogeneous group. This limitation speaks not only to challenges in identifying the degree of impairment expected, but also, to some extent, in the specific nature of the impairments which can be anticipated given the variability in symptom presentation in these patients. In an attempt to address the limits of group statistics, some authors have identified the level of impairment in each patient studied. For example, as described in greater detail in the review of the controlled studies, Krupp et al. (1991) divided the Lyme group by level of impairment and found that 9 of the 15 patients studied were impaired by their criteria. Most of those 9 patients were described as "moderately" impaired, though clearly there was substantial variability within the group. Several other researchers have commented on the percentage of patients within the group who perform below a specified cutoff for impairment on a given measure (e.g., Svetina et al., 1999), though variability in the extent of impairment is often not reported. Preliminary data from our own study examining the relationship between cognitive functions and psychological factors such as depression, anxiety, fatigue, and tolerance for mental effort in 17 patients with Lyme disease (including 12 with multiple tick-borne diseases) and 17 healthy controls (Westervelt

and McCaffrey, 1999) provide evidence of the variability in symptom severity and presentation. For example, in our sample, the Lyme group's performance was significantly worse than that of the control group's on the PASAT. On this measure, 10 of 17 patients (59%) in the Lyme group exhibited impairment (a score $\geq$1 *SD* below the mean of the control group). This included 1 patient with mild impairment (1–1.4 *SD* below the control mean), 2 with moderate impairment (1.5–1.9 *SD* below the control mean), and 7 with severe impairment ($\geq$2 *SD* below the control mean). The Lyme group also performed significantly worse than did the control group on phonemic verbal fluency (FAS), including 9 patients with impaired performance. In contrast with the prior example, however, most patients showed only mild impairment on this measure ($N = 7$), only 2 showed moderate impairment, and none were severely impaired. Even on tasks for which no significant group differences were observed, the Lyme patients were often at least twice as likely to show impairments, though patients who were impaired on one measure may not have been the same patients who were impaired on another, arguing against the presence of global impairment in the subset of impaired patients. Thus, given the variability in group findings from one study to another, closer attention to the presentation of individual patients within each study may be beneficial in understanding the range of intensity of symptom severity and variety of impairments which can be observed in this disease. This suggests that, in contrast with other neuropsychological disorders such as Alzheimer's disease, there may not be a "classic" neuropsychological pattern in Lyme disease, though some impairments certainly appear more often than others. Lastly, the possibility that the variability in symptom presentation and severity is perhaps in part a reflection of different underlying mechanisms (e.g., persisting CNS infection vs. an inflammatory response or immune reaction) is worth considering. This raises the possibility that the groups studied are less homogeneous than assumed, again making generalizations difficult.

Other limitations in the current neuropsychological literature on Lyme disease include the use of very small samples. Apparently, the effect sizes are robust enough to yield significant findings in many instances regardless of the small samples, though low statistical power makes the likelihood of discovering more modest deficits unlikely. In addition, given the small size of the samples, outliers in either direction may have a substantial impact on group statistics. This also limits the extent to which findings can be generalized, though, as previously mentioned, the ability to make global statements in this group is difficult, given the variability of patient presentations.

### Impact of Chronic Illness

It is noteworthy that several of the controlled studies used patient control groups, including groups with depression (Kaplan et al., 1992), fibromyalgia (Kaplan et al., 1992), neurologic dysfunction without brain damage (Benke et al., 1995), osteomyelitis (Ravdin et al., 1996), and CFS (Gaudino et al., 1997). Except for comparison with osteomyelitis patients, in each study providing direct comparisons, the group with Lyme disease performed poorer than the other patient groups on several measures of neuropsychological functioning. In addition to these controlled studies, in a brief report, Gasse et al. (1992) described the neuropsychological functioning in 15 patients who had been treated for Lyme disease and had recovered *neurologically*, compared with both healthy controls and patients who had suffered from viral meningitis/encephalitis. The results showed impaired verbal learning in both patient groups, though the participants with histories of Lyme disease had more extensive findings, including deficits on word-list generation and syllable repetition. Measures of psychomotor speed, sustained attention, visuo-spatial ability, and other aspects of executive functioning were reportedly normal. Taken together, these studies indicate that the deficits observed in the groups with Lyme disease cannot be solely attributed to the presence of a chronic illness.

### Relationship with Depression

As noted in previous sections, depression is a fairly frequently reported problem in chronic Lyme disease. Given the known cognitive effects of depression, several of the controlled neuropsychological studies of Lyme disease have considered the possible impact of depression on neuropsychological functioning. The nature of the observed relationship, however, has been somewhat surprising. Two of the nine controlled studies examining the relationship between depression and cognition found significant *positive* correlations between depression and memory performance, indicating that an increase in depression scores was associated with *better* memory functioning (Gaudino et al., 1997; Krupp et al., 1991). In contrast, Bujak et al. (1996), Kaplan et al. (1999), Pollina, Elkins, et al. (1999); Pollina, Sliwinski, et al. (1999), Ravdin et al. (1996), and Svetina et al. (1999) found no relationship between objective memory performance and depression, though Ravdin et al. (1996) noted that depression was significantly correlated with *subjective perception* of cognitive loss. Finally, Kaplan et al. (1992) found a *negative* correlation, though with only one measure of memory (WMS-R Associate

Learning). It should also be noted that although Kaplan et al. (1999) found no relationship between depression and neuropsychological functioning, they did find some relationship between state anxiety and slower reaction time in a post-Lyme group, though there was no relationship between anxiety and neuropsychological performance in the Lyme encephalopathy group.

In two recent studies, the relationship between mood states and neuropsychological performance has been more directly addressed. Barr et al. (1999) examined 55 patients at the time of their initial diagnosis with Lyme disease. All patients were administered the Self-Ratings of Memory Questionnaire, the BDI, and the CVLT. On the self-report memory measure, the group complained most of an inability to recall names, hold information in memory, and recall what one was doing, as well as a lack of confidence that information will be retained. They did not describe a general sense of confusion or difficulty with remote memory. Patients with depression (as defined by a BDI score of greater than 10) endorsed relatively more items suggesting memory complaints than did non-depressed patients, though there was no distinguishable pattern to the items that were endorsed. The majority of the patients rated their memory as worse than before. It should be noted that most of the scores on the BDI were below the level associated with depression. Specifically, when the groups were divided according to BDI scores, 63.6% reported minimal depression (BDI scores of 0–9), 25% of the group was within the mild range (BDI scores of 10–16), and only 10% was within the moderate to severe range (BDI scores of 17–30). Significant correlations were found between the self-report memory questionnaire and the BDI scores ($p = -.57$), in that patients endorsing more depressive symptoms also reported having poorer memory functioning. In contrast, there was no significant relationship between BDI scores and performance on the CVLT, or between CVLT performance and measures of subjective memory loss. Furthermore, on the CVLT, the three depression groups did not differ in their performances on total learning and delayed recall, and the mean scores for all groups fell within the average range compared with normative standards. Individual patients whose memory scores were lower than one standard deviation below the mean of the normative data showed no tendency to underreport symptoms of memory disturbance, arguing against anosognosia in patients with weaker memory performance.

Elkins et al. (1999) characterized the psychological status of a group of 30 post-Lyme patients (all with documented neurologic symptoms at the time of initial diagnosis) and examined the relationship between reported symptoms and neuropsychological performance. They screened for the presence of current and lifetime *DMS-IV* Axis I diagnoses, as well as examining positive and negative mood states by using the Positive and Negative Affect Schedule (PANAS). The authors note that positive and negative affect have been useful in distinguishing affective states associated with psychiatric disorders. Specifically, they state that depressive disorders are characterized by low positive affect and heightened negative affect, whereas anxiety disorders are associated with heightened negative affect alone. They also note that previous studies have shown that CFS is characterized by low positive affect, and in these patients, low positive affect has been related to cognitive and motor slowing. Elkins et al. also examined cognitive performance in their post-Lyme group by using a variety of neuropsychological measures (WAIS-R Vocabulary, Block Design, Digit Span, and Digit Symbol, Wide Range Achievement Test-Revised Reading, WMS-R Logical Memory story A or B, SRT, PASAT, and TMT). Results showed that 37% of the participants met current criteria for a *DSM-IV* Axis I disorder, and 50% met lifetime criteria for an Axis I disorder, though only 20% met criteria for a disorder before the onset of their Lyme disease. Elkins et al. state that although the percentage of participants meeting the lifetime criteria for an Axis I disorder is comparable with that in the general population, it may be noteworthy that the incidence of an Axis I disorder nearly doubled following the onset of Lyme disease in this group. On the PANAS, the group had significantly lower levels of positive affect compared with published norms, but comparable negative affect levels. As discussed, this pattern differs from that typically seen in major depression, and the authors speculate that low positive affect in this group may reflect the impact of fatigue on pleasant and active engagement with one's environment. Positive and negative affect were not significantly correlated, nor were they associated with the presence of a current psychiatric disorder. In contrast, low levels of positive affect corresponded to subjective illness severity, but not with objective indicators of the course and nature of the disease process itself (e.g., duration of illness, the presence of neurologic symptoms at the time of diagnosis, or antibiotic treatment history). The cognitive measures were clustered into four areas of functioning: (1) general intelligence, (2) attention, (3) verbal learning, and (4) psychomotor speed. Compared with normative data, the group's performance was not impaired (i.e., it was not more than one standard deviation below the normative mean), though the PASAT and SRT approached this level (–0.88 to –0.99 *SD* below the mean). In multiple regression analyses, none of the psychological measures significantly predicted cognitive performance in any of the four domains. Although limited by lack of a comparison group, this study provides

interesting data by demonstrating not only a lack of association between current depressive symptoms and neuropsychological functioning as other studies have, but also a lack of association between other mood states and the presence of current and life-time Axis I disorders.

Kaplan and Jones-Woodward (1997) point out that although the literature has demonstrated that depression ratings are often higher in patients with Lyme disease relative to controls, the average depression scores in the Lyme groups are often below the suggested cutoff for clinically significant depression. In addition, as noted earlier in this section, the one study directly comparing patients with Lyme disease and healthy depressed controls found that the Lyme group performed significantly worse on neuropsychological measures than did the depressed controls. Therefore, the general lack of significant negative correlations between depression scores and neuropsychological functioning in these patients may not be surprising. However, Kaplan and Jones-Woodward note that the stress and anxiety associated with chronic illness may be a factor in *perceived* memory disturbance, even though these patients may not be *clinically* depressed. The possibility that the presence of depression-like symptoms may better reflect fatigue or other physical symptoms of the disease is also worth considering, particularly given that the one study that examined only the "cognitive" (i.e., nonphysical) aspects of depression found no difference between the Lyme patients and controls. Thus, overall, depression or depression-like symptoms do *not* appear to be causally related to objective neuropsychological impairment in Lyme disease, though they may be related to the perception of cognitive loss.

The importance of identifying neuropsychological impairments as being *causally related* to other symptoms such as depression versus being *independent symptoms*, which may often occur together as part of the same underlying pathology, is not just semantic. Rather, it may have important implications. First, although seldom discussed in the literature, there tends to be some debate among clinicians regarding the etiology of chronic Lyme disease/post-Lyme syndrome, particularly the neuropsychological deficits/complaints. Bujak et al. (1996) hint at this debate by indicating that it is unknown whether personality factors may predispose patients to post-Lyme syndrome. This statement suggests that some may view chronic Lyme/post-Lyme syndrome as a primarily psychiatric disturbance, or at least as involving a strong psychiatric component. This perception may greatly impact the treating clinician's view of the patient, as well as their willingness to consider the need for further treatment or type of treatment to be recommended. Although psychiatric conditions should certainly be addressed, this should not occur at the exclusion of consideration of other appropriate medical treatments or cognitive remediation, when indicated.

### Relationship with Neurologic Indicators of Disease

The relationship between neurocognitive functioning and neurologic status is unclear. In a brief report, Kaplan et al. (1995) first attempted to elucidate this relationship by comparing memory functioning on the SRT in healthy controls ($n = 11$) to Lyme patients with ($n = 16$) and without ($n = 21$) increased CSF protein and/or intrathecal antibody production. They found that the patients with abnormal CSF scored significantly worse on the SRT. They interpreted these findings as suggesting that memory loss is caused by CNS infection, as evidenced by CSF abnormalities. Similarly (as described in greater detail in a previous section), in a full report directly investigating this issue, Kaplan et al. (1999) compared the neuropsychological performance in chronic Lyme patients with and without objective evidence of persistent CNS infection. They found that only the group with objective encephalopathic symptoms demonstrated memory impairment. The "post-Lyme" group (those without objective evidence of CNS dysfunction) performed worse on a measure of reaction time on a vigilance task, though the authors speculated that this deficit was likely due to increased anxiety in this group. In contrast, however, Pollina, Sliwinski, et al. (1999) refer to preliminary data comparing cognitive processing speed and memory in Lyme patients with and without CNS evidence of infection, which showed no significant group difference. Furthermore, in other studies discussed in prior sections, statistically significant differences in cognitive functioning were found in Lyme patients relative to healthy controls, even when none of the patients in the Lyme sample showed CSF evidence of persisting disease (e.g., Ravdin et al., 1996).

Although not the primary focus of most of the neuropsychological studies reported in the literature, several investigators have attempted more peripherally to address this issue by including MRI or CSF findings when available. For example, Krupp et al. (1991) note that among their sample of 15 Lyme patients, 8 underwent neuroimaging via MRI. Two of these patients, both of whom were described as cognitively impaired, had scans that revealed one or more small areas of increased signal intensity in the subcortical white matter on T2-weighted images, though overall, Krupp et al. stated that MRI findings were not predictably related to neurocognitive findings. Similarly, antibody levels in serum and CSF (the latter presumably

reflective of CNS infection) had no relationship to neuropsychological functioning. Logigian et al. (1990) describe neuropsychological functioning in 27 Lyme patients with chronic neurologic abnormalities, including 18 participants with CSF evidence of Lyme disease. They found that only half of the patients with abnormal CSF findings showed objective memory impairment according to published normative data. In contrast, among the 19 patients who underwent MRI imaging, 5 had abnormal scans consisting of numerous small areas of increased T2-signal intensity primarily in the peripheral white matter, and all 5 of these patients showed evidence of objective memory impairment.

In sum, the relationship between neurologic evidence of *active* CNS involvement, particularly via CSF findings, and neuropsychological functioning remains unclear. To date, the one controlled study examining this issue suggests that patients with evidence of active CNS infection are more likely to show cognitive impairment than those without (Kaplan et al., 1999). However, other evidence demonstrates that although positive neurologic findings are often associated with neuropsychological dysfunction, negative imaging or CSF studies are not necessarily indicative of normal neuropsychological functioning. It is possible that among cognitively impaired patients without evidence of active CNS infection, other factors account for the observed neuropsychological impairment (e.g., inflammatory or immune reactions; prior invasion of the CNS resulting in irreversible damage that can be objectively observed on neuropsychological measures and, in some instances, neuroimaging studies).

### Relationship to Fatigue

Fatigue appears to be a common symptom in chronic Lyme disease. In fact, a recent study by Treib et al. (2000) suggests that fatigue may be the sole manifestation of the illness. The relationship between fatigue and neuropsychological symptoms, however, has remained an unclear and debated issue.

Three of the four controlled studies measuring fatigue found a significant negative correlation between fatigue and memory performance (Krupp et al., 1991; Pollina, Sliwinski, et al., 1999; Ravdin et al., 1996), and the fourth did not examine the relationship (Gaudino et al., 1997). However, whether a causal relationship exits is unclear. Pollina, Sliwinski, et al. (1999) suggest that "some of the memory deficits are the result of noncognitive factors such as fatigue" (p. 77). Kaplan and Jones-Woodward (1997) also state that "tasks requiring sustained effort, like the CVLT, may be more vulnerable to the effects of fatigue, and Lyme patients do report greater fatigue than controls" (p. 34). Presumably, the assumption is that the amount of effort Lyme patients are able to exert is limited by the extent of their fatigue, and that this reduced ability to sustain effort results in poorer performance on some neuropsychological measures. Given that the tasks at which chronic Lyme patients often fail tend to be particularly effortful, this hypothesis is reasonable. However, given the finding that Lyme patients appear to show greater neuropsychological impairment than do patients with CFS (Gaudino et al., 1997), it is plausible that these symptoms often occur together without being causally related. That is, fatigue and cognitive impairment may represent independent symptoms of the same underlying process that co-vary in intensity as a function of disease severity.

Preliminary data from our laboratory (described briefly above) support the latter hypothesis (Westervelt and McCaffrey, 1999). We examined the relationship between performance on neuropsychological measures (CVLT, PASAT, FTT, grooved pegboard, COWA, and Word Attack subtest from the Woodcock–Johnson Psychoeducational Battery—Revised) and fatigue (Fatigue Severity Scale), depression (BDI), anxiety (State Trait Anxiety Inventory), and tolerance for mental effort (Mental Effort Tolerance Questionnaire; Dornic et al., 1991). We hypothesized that if fatigue were causally related to neuropsychological performance, tolerance for mental effort would be the mediating variable. Although the Lyme patients performed more poorly than did the controls on a number of neuropsychological measures (PASAT, FAS, and number of perseverative responses on the CVLT) and also endorsed more depression, anxiety, fatigue, and intolerance for mental effort, there were no statistically significant relationships between any of the psychological and neurocognitive measures in the Lyme group. In addition, there was no significant relationship between fatigue and tolerance for mental effort in the Lyme group.

It should be noted that although our study results call into question the assumption of a direct causal relationship between fatigue and neuropsychological performance, the impact of chronic fatigue on the ability to persistently provide cognitive effort is likely more complicated than our study suggests and needs to be further considered. Fatigued patients in clinical practice often note that they feel able to "rise to the occasion" during the course of a testing session, though they often complain of feeling mentally depleted following the exam and state that they would be unable to provide that level of effort on a consistent basis. In an elegant recent study, Krupp and Elkins (2000) investigated the impact of prolonged cognitive

exertion on neuropsychological test performance in another fatiguing illness—MS. In their study, Krupp and Elkins examined the impact of cognitive fatigue by administering a neuropsychological battery twice—once before and once after the administration of a continuous cognitively effortful task (the Alphabetic–Arithmetic Test). Alternate forms were used when possible to minimize the effects of prior exposure. Results showed that the MS patients ($N = 45$) and controls ($N = 14$) did not differ in their neuropsychological performance at baseline. However, following the continuous mental exertion task, the MS patients' performance declined on measures of verbal list-learning (SRT), visual memory (10/36 Spatial Recall Test), and executive functioning (Tower of Hanoi), whereas the control patients' performance improved. Changes in scores showed statistically significant declines in the MS group on aspects of the SRT and Tower of Hanoi, with statistically significant improvement on these measures in the control group. Performance between the groups following the exertion task was significantly different on the SRT, visual memory task, and COWA. Krupp and Elkins also examined performance during the mental exertion task and found that there were no differences between groups on the first half of the task, though the MS group had slower reaction times during the second half. Of note, measures of state mood and fatigue were administered throughout the exam. Although both groups described experiencing increasing cognitive and physical fatigue throughout the testing session, only the MS group demonstrated evidence of objective fatigue.

These findings provide an excellent illustration of some of the complexities in studying the relationship between fatigue and cognitive performance. In the example above, the fatigued and control groups did not differ significantly at baseline, suggesting that in at least some fatigued patients, the detrimental impact of cognitive exertion may not be readily seen on initial exam. These findings also hint at the possibility that deficits that may be apparent *before* fatigued patients are asked to provide continuous, sustained effort are less likely a reflection of their fatigue than other factors. Furthermore, this study suggests that the kind of tasks that are most likely to induce more widespread cognitive problems due to fatigue may be rather specific—that is, tasks requiring prolonged and constant effort. Lastly, the extent of decline due to fatigue in this study needs to be underscored. It is notable that not only the fatigued patients performed worse than did the controls following the continuous effort task, but also that their performance deteriorated. This suggests that the degree of fatigue was significant enough to offset any benefits of prior exposure to the testing materials presented earlier in the same-day session.

**Treatment Effects**

In most patients, early treatment with oral antibiotics can successfully shorten the course of early symptoms and reduce the likelihood of later complications (Athreya and Rose, 1996; Reik et al., 1986; Steere, 2001). Typical agents for treating acute early disease include doxycycline and amoxicillin (Halperin, 1999), though other antibiotics may also be effective. In approximately 14% of patients, typically in those with more severe disease, symptoms may initially worsen with the advent of antibiotic treatment before improvement is seen, a phenomenon similar to the Jarisch–Herxheimer reaction that can occur in the antibiotic treatment of syphilis (Burrascano, 1989). Patients who do not respond to oral antibiotics or those with symptoms of later disease may respond to intravenous antibiotic therapy (Fallon et al., 1995; Finkel and Halperin, 1992). Ceftriaxone is commonly used intravenously to treat chronic, particularly neurologic, symptoms (Halperin, 1999). It remains controversial whether prolonged antibiotic treatment is beneficial in previously treated patients with persisting symptoms. A recent randomized trial suggests that additional 90-day treatment of intravenous and oral antibiotics does not improve symptoms more than placebo (Klempner et al., 2001). Those who are not treated at all until later in the disease may be more likely to develop chronic disorders, including neuropsychological impairment, than those treated early in the disease (Fallon et al., 1995).

The reversibility of neuropsychological deficits following treatment has been evaluated in two studies. Halperin et al. (1988) examined 17 patients with presumably previously untreated, late Lyme disease (mean duration of disease = 32.6 months) complaining of poor memory or other cognitive difficulties. Of these patients, 4 presented with other neurologic involvement, and 1 had abnormal CSF findings. All patients were tested before antibiotic treatment and retested 5–28 weeks following treatment. Significant improvement was found on tests of verbal and visual recall, a test of problem solving (Booklet Category Test), and measures described by the authors as indicators of psychomotor speed (WAIS-R Block Design and Purdue Pegboard). Although Halperin et al. attempted to control for practice effects across assessments by using alternate forms with the CVLT and WMS, without the comparison of a control group, the relative contributions of practice/test sophistication and improvements in cognitive functioning due to treatment effects are almost impossible to tease apart (McCaffrey et al., 2000; McCaffrey and Westervelt, 1995). The possible impact of practice effects/test sophistication may be of particular concern in the current study, as all of the measures that

showed improvement are among those considered most likely to be affected by practice [i.e., memory tasks, tasks with a single, easily conceptualized response, and tasks with a speeded component (Lezak, 1995)].

Pass et al. (1987) describe 8 patients with Lyme disease who were also tested with a battery of neuropsychological instruments both before and after antibiotic treatment. Pass et al. similarly found significant improvement on most measures of cognitive functioning after treatment. Tests measuring memory, attention, and problem solving were most improved. As with the Halperin et al. (1989) study, however, no control group was included, and the relative contributions of practice and recovery cannot be determined. However, given that brain lesions detected on MRI and perfusion defects as seen on SPECT have been found to be reversible (Halperin et al., 1989; Logigian et al., 1997), the possibility that cognitive deficits may also reverse or at least improve seems plausible, though controlled studies are required to document the extent of the recovery. As suggested in previous sections, however, the etiology of chronic deficits is unclear. If, as many researchers suggest, persisting symptoms in patients who have been previously adequately treated are not reflective of chronic, active infection, then the underlying cause of these symptoms must be determined if appropriate treatments are to be identified.

## SUMMARY AND FUTURE DIRECTIONS

Over the past decade, the nature and extent of the neuropsychological deficits in Lyme disease have just begun to be elucidated in controlled studies. With some consistency, patients with chronic Lyme disease have demonstrated generally mild deficits in some aspects of verbal memory (particularly list-learning), verbal fluency, upper extremity fine motor speed/coordination and oral agility, and speed of information processing, though the extent and nature of impairments is somewhat variable. However, overall the nature of these deficits is generally consistent with what can be seen in other disorders with primarily frontal systems involvement, including many autoimmune disorders. Indeed, the autoimmune disorders, particularly those involving fatigue, may provide a good conceptual framework within which to consider the assessment of cognitive functioning in chronic Lyme disease, given the high degree of symptom overlap among these disorders (e.g., fatigue and other physical concerns, cognitive complaints, psychiatric findings, and, in some cases, relapsing and remitting course). Some investigators have found correlations between neuropsychological functioning and findings on neuroimaging studies. However, the nature of the relationship between direct indicators of active CNS infection via CSF analysis and neuropsychological functioning remains elusive. Although there is some evidence to suggest that patients with evidence of active CNS infection are more likely to show cognitive impairment than those without, patients without evidence of active infection can nevertheless demonstrate neuropsychological deficits.

In addition to demonstrated neuropsychological deficits, chronic Lyme patients have also often shown affective symptoms and fatigue. Although there appears to be little relationship between objective neuropsychological functioning and affective symptoms such as depression, depression may be related to the perception of cognitive loss. In contrast, most studies examining the relationship between fatigue and neurocognitive functioning have found a significant negative correlation. The relationship between fatigue and cognitive functioning, however, is likely complex, and it is unclear whether a causal relationship exists, or if these are independent symptoms of the same underlying disease process. Lastly, there have been no controlled empirical studies examining the impact of antibiotic treatment on neuropsychological functioning, though two case series suggest that these deficits may be at least partially reversible with appropriate antibiotic therapy. The possible benefits of behavioral treatments such as cognitive remediation have not yet been empirically explored. However, the possibility that patients with chronic Lyme disease may benefit from cognitive rehabilitation merits consideration for treatment options, as well as for a topic of future scientific investigation. Further research designed to more fully understand the relationship between neuropsychological functioning and neurologic indicators of disease and fatigue is clearly needed, as are controlled pharmacologic and behavioral treatment studies. Furthermore, Lyme patients often report that their cognitive symptoms relapse and remit, at times in conjunction with additional antibiotic treatment. Therefore, longitudinal studies may be helpful not only in determining the extent to which neuropsychological impairments respond to treatment, but also in identifying factors relating to relapse and remission. Important considerations in treatment studies also include the uncertain etiology of persisting impairments. It has been speculated that the heterogeneity in symptom presentation in patients with persisting impairment may reflect different underlying etiologies. Clearly, an understanding of the cause of these symptoms will be critical to both clarifying why symptoms persist in some patients with Lyme disease, as well as, and more importantly, identifying how to treat these symptoms.

Lastly, newer problems, including the increasing number of patients with multiple tick diseases (in

particular, babesiosis and human granulocytic ehrlichiosis [HGE]) have surfaced. Some investigators suggest that the rate of coinfection with HGE in patients with Lyme disease may be as high as one in five in some endemic areas (De Martino et al., 2001). To date, however, there have been few published studies examining the impact of multiple tick diseases on overall functioning, and those which exist are inconsistent (Wang et al., 2000). Furthermore, there have been no published studies examining neuropsychological sequelae in either babesiosis or HGE alone, or in combination with Lyme disease.

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## REFERENCES

Ackermann, R., Horstrup, P., and Schmidt, R. (1984). Tick-borne menigopolyneuritis (Garin-Bujadoux, Bannwarth). *Yale J. Biol. Med.* **57:** 485–490.

Ackermann, R., Rehse-Kupper, B., Gollmer, E., and Schmidt, R. (1988). Chronic manifestations of erythema migrans borreliosis. *Ann. N. Y. Acad. Sci.* **539:** 16–23.

Adams, W. V., Rose, C. D., Eppes, S. C., and Klein, J. D. (1994). Cognitive effects of Lyme disease in children. *Pediatrics* **94:** 185–189.

Adams, W. V., Rose, C. D., Eppes, S. C., and Klein, J. D. (1999). Long-term cognitive effects of Lyme disease in children. *Appl. Neuropsychol.* **6:** 39–45.

Athreya, B. H., and Rose, C. D. (1996). Lyme disease. *Curr. Probl. Pediatr.* **26:** 189–207.

Bakken, L. L., Case, K. L., Callister, S. M., Bourdeau, N. J., and Schell, R. F. (1992). Performance of 45 laboratories participating in a proficiency testing program for Lyme disease serology. *JAMA* **268:** 891–895.

Barr, W. B., Rastogi, R., Ravdin, L., and Hilton, E. (1999). Relations among indexes of memory disturbance and depression in patients with Lyme disease. *Appl. Neuropsychol.* **6:** 12–18.

Benke, Th., Gasse, Th., Hittmair-Delazer, M., and Schmutzard, E. (1995). Lyme encephalopathy: long-term neuropsychological deficits years after acute neuroborreliosis. *Acta Neurol. Scand.* **91:** 353–357.

Bloom, B. J., Wyckoff, P. M., Meissner, C., and Steere, A. C. (1998). Neurocognitive abnormalities in children after classic manifestations of Lyme disease. *Pediatr. Infect. Dis. J.* **17:** 189–196.

Broderick, J. P., Sandok, B. A., and Mertz, L. D. (1987). Focal encephalitis in a young woman 6 years after the onset of Lyme disease: Tertiary Lyme disease? *Mayo Clin. Proc.* **62:** 313–316.

Bujak, D. I., Weinstein, A., and Dornbush, R. L. (1996). Clinical and neurocognitive features of the post Lyme syndrome. *J. Rheumatol.* **23:** 1392–1397.

Burgdorfer, W. (1991). Lyme borreliosis: tenTen years after the discovery of the etiologic agent, *Borrelia burgdorferi*. *Infection* **19:** 257–262.

Burgdorfer, W., Barbour, A. G., Hayes, S. F., Benach, J. L., Grunwaldt, E., and Davis, J. P. (1982). Lyme disease: A tick borne spirochete? *Science* **216:** 1317–1319.

Burrascano, J. (1989). Late-stage Lyme disease: Treatment options and guidelines. *Intern. Med.* **10:** 102–107.

Caliendo, M. V., Kushon, D. J., and Helz, J. W. (1995). Delirium and Lyme disease. *Psychosomatics* **36:** 69–74.

Centers for Disease Control (1991). Lyme disease surveillance: United States, 1989–1990. *MMWR* **40:** 417–421.

Centers for Disease Control (1995). Summary of notifiable diseases, United States, 1995. *MMWR* **44:** 6, 10–11, 41, 73–74.

Coyle, P. K. (1992). Neurologic Lyme disease. *Semin. Neurol.* **12:** 200–208.

De Martino, S. J., Carlyon, J. A., and Fikrig, E. (2001). Coinfection with *Borrelia burgdorferi* and the agent of human granulocytic ehrilichiosis. *N. Engl. J. Med.* **345:** 150–151.

Dornic, S., Ekehammer, B., and Laaksonen, T. (1991). Tolerance for mental effort: Self-ratings related to perception, performance, and personality. *Person. Individ. Diff.* **12:** 313–319.

Elkins, L. E., Pollina, D. A., Scheffer, S. R., and Krupp, L. B. (1999). Psychological states and neuropsychological performances in chronic Lyme disease. *Appl. Neuropsychol.* **6:** 19–26.

Fallon, B. A., Das, S., Plutchok, J. J., Tager, F., Liegner, K., and Van Heertum, R. (1997). Functional brain imaging and neuropsychological testing in Lyme disease. *Clin. Infect. Dis.* **25**(Suppl 1)**:** S57–63.

Fallon, B. A., Kochevar, J. M., Gaito, A., and Nields, J. A. (1998). The underdiagnosis of neuropsychiatric Lyme disease in children and adults. *Psychiatr. Clin. North Am.* **21:** 693–703.

Fallon, B. A., and Nields, J. A. (1994). Lyme disease: A neuropsychiatric illness. *Am. J. Psychiatry* **151:** 1571–1583.

Fallon, B. A., Nields, J. A., Burrascano, J. J., Liegner, K., DelBene, D., and Liebowitz, M. R. (1992). The neuropsychiatric manifestations of Lyme borreliosis. *Psychiatr. Q.* **63:** 95–115.

Fallon, B. A., Nields, J. A., Parsons, B., Liebowitz, M. R., and Klein, D. F. (1993). Psychiatric manifestations of Lyme borreliosis. *J. Clin. Psychiatry* **54:** 263–268.

Fallon, B. A., Schwartzberg, M., Bransfield, R., Zimmerman, B., Scotti, A., Weber, A., et al. (1995). Late-stage neuropsychiatric Lyme borreliosis. Differential diagnosis and treatment. *Psychosomatics* **36:** 295–300.

Finkel, M. J., and Halperin, J. J. (1992). Nervous system Lyme borreliosis—revisited. *Arch. Neurol.* **49:** 102–107.

Fletcher, P. C., Frith, C. D., Grasby, P. M., Shallice, T., Frackowiak, R. S., and Dolan, R. J. (1995). Brain systems for encoding and retrieval of auditory-verbal memory. An in vivo study in humans. *Brain* **118:** 401–416.

Garcia-Monoco, J. C., Villar, B. F., Alen, J. C., and Benach, J. L. (1990). *Borrelia burgdorferi* in the central nervous system: Experimental and clinical evidence for early invasion. *J. Infect. Dis.* **161:** 1187–1193.

Gasse, Th., Hittmar, M., Schmutzhard, E., and Benke, Th. (1992). Neuropsychology of late Lyme disease. *J. Clin. Exp. Neuropsychol.* **14:** 384.

Gaudino, E. A., Coyle, P. K., and Krupp, L. B. (1997). Post-Lyme syndrome and chronic fatigue syndrome. Neuropsychiatric similarities and differences. *Arch. Neurol.* **54:** 1372–1376.

Grasby, P. M., Frith, C. D., Friston, K. J., Bench, C., Frackowiak, R. S., and Dolan, R. J. (1993). Functional mapping of brain areas implicated in auditory-verbal memory function. *Brain* **116:** 1–20.

Halperin, J. J. (1999). Neuroborreliosis (Nervous system Lyme disease). *Curr. Treat. Options Neurol.* **1:** 139–145.

Halperin, J. J. (2000). Nervous system Lyme disease. *Infect. Med.* **17:** 556–560.

Halperin, J. J., Luft, B. J., Anand, A. K., Roque, C. T., Alvarez, O., Volkman, D. J., et al. (1989). Lyme neuroborreliosis: centralCentral nervous system manifestations. *Neurology* **39:** 753–759.

Halperin, J. J., Pass, H. L., Anand, A. K., Luft, B. J., Volkman, D. J., and Dattwyler, R. J. (1988). Nervous system abnormalities in Lyme disease. *Ann. N. Y. Acad. Sci.* **539:** 24–34.

Kaplan, R. F., Jones, L. C., Meadows, M. E., Logigian, E., and Steere, A. C. (1995). CNS infection and memory disturbance in Lyme disease. *J. Int. Neuropsychol. Soc.* **1:** 347.

Kaplan, R. F., and Jones-Woodward, L. (1997). Lyme encephalopathy: A neuropsychological perspective. *Semin. Neurol.* **17:** 31–37.

Kaplan, R. F., Jones-Woodward, L., Workman, K., Steere, A. C., Logigian, E. L., and Meadows, M. E. (1999). Neuropsychological deficits in Lyme disease patients with and without other evidence of central nervous system pathology. *Appl. Neuropsychol.* **6:** 3–11.

Kaplan, R. F., Meadows, M. E., Vincent, L. C., Logigian, E. L., and Steere, A. C. (1992). Memory impairment and depression in patients with Lyme encephalopathy: Comparison with fibromyalgia and nonpsychotically depressed patients. *Neurology* **42:** 1263–1267.

Karussis, D., Weiner, H. L., and Abramsky, O. (1999). Multiple sclerosis vs Lyme disease: A case presentation to a discussant and a review of the literature. *Mult. Scler.* **5:** 395–402.

Klempner, M. S., Hu, L. T., Evans, J., Schmid, C. H., Johnson, G. M., Trevino, R. P., et al. (2001). Two controlled trials of antibiotic treatment in patients with persistent symptoms and a history of Lyme disease. *N. Engl. J. Med.* **345:** 85–92.

Kobayaski, K., Mizukoshi, C., Aoki, T., Muramori, F., Hayashi, M., Miyazu, K., et al. (1997). *Borrelia burgdorferi*-seropositive chronic encephalomyelopathy: Lyme neurroborreliosis? An autopsied report. *Dement. Geriatr. Cogn. Disord.* **8:** 384–390.

Kohler, V. J., Kern, U., Kasper, J., Rhese-Kupper, B., and Thoden, U. (1988). Chronic central nervous system involvement in Lyme borreliosis. *Neurology* **38:** 863–867.

Krupp, L. B., and Elkins, L. E. (2000). Fatigue and declines in cognitive functioning in multiple sclerosis. *Neurology* **55:** 934–939.

Krupp, L. B., Masur, D., Schwartz, J., Coyle, P. K., Langenbach, L. J., Fernquist, S. K., et al. (1991). Cognitive functioning in late Lyme borreliosis. *Arch. Neurol.* **48:** 1125–1129.

Lastavica, C. C., Wilson, M. L., Berardi, V. P., Spielman, A., and Deblinger, R. D. (1989). Rapid emergence of a focal epidemic of Lyme disease in coastal Massachusetts. *N. Engl. J. Med.* **320:** 133–137.

Lezak, M. D. (1995). *Neuropsychological Assessment* (3rd Ed.), Oxford University Press, New York.

Liegner, K. B. (1993). Lyme disease: The sensible pursuit of answers. *J. Clin. Microbiol.* **31:** 1961–1963.

Logigian, E. L., Johnson, K. A., Kijewski, M. F., Kaplan, R. F., Becker, J. A., Jones, K. J., et al. (1997). Reversible cerebral hypoperfusion in Lyme encephalopathy. *Neurology* **49:** 1661–1670.

Logigian, E. L., Kaplan, R. F., and Steere, A. C. (1990). Chronic neurologic manifestations of Lyme disease: Encephalopathy, polyneuropathy, and leukoencephalitis. *N. Engl. J. Med.* **323:** 1438–1444.

MacDonald, A. B., and Miranda, J. M. (1987). Concurrent neocoritcal borreliosis and Alzheimer's disease. *Hum. Pathol.* **18:** 759–761.

Masur, D., Krupp, L., Coyle, P., Halperin, J., Jandorf, L., and Schwartz, J. (1992). Persistent memory deficits in Lyme disease. *J. Clin. Exp. Neuropsychol.* **14:** 58–59.

McCaffrey, R. J., Duff, K., and Westervelt, H. J. (2000). *Practitioner's Guide to Evaluating Change with Neuropsychological Assessment Instruments*, Plenum Press, New York.

McCaffrey, R. J., and Westervelt, H. J. (1995). Issues associated with repeated neuropsychological assessments. *Neuropsychol. Rev.* **5:** 203–221.

Melski, J. W. (1999). Language, logic, and Lyme disease. *Arch. Dermatol.* **135:** 1398–1400.

Midgard, R., and Hofstad, H. (1987). Unusual manifestations of nervous system *Borrelia burgdorferi* infection. *Arch. Neurol.* **44:** 781–783.

Miklossy, J., Kuntzer, T., Bogousslavsky, J., Regli, F., and Janzer, R. C. (1990). Meningovascular form of neuroborreliosis: Similarities between neuropathologic findings in a case of Lyme disease and those occurring in tertiary neurosyphilis. *Acta Neuropathol. (Berl.)* **80:** 568–572.

Nields, J. A., and Kveton, J. F. (1991). Tullio phenomenon and seronegative Lyme borreliosis. *Lancet* **338:** 128–129.

Oksi, J., Kalimo, H., Marttila, R. J., Marjamaki, M., Sonninen, P., Nikoskelainen, J., et al. (1996). Inflammatory brain changes in Lyme borreliosis. A report on three patients and review of the literature. *Brain* **119:** 2143–2154.

Oksi, J., Viljanen, M. K., Kalimo, H., Peltonen, R., Martila, R., Salomaa, P. L., et al. (1993). Fetal encephalitis caused by concomitant infection with tick-borne encephalitis virus and *Borrelia burgdorferi*. *Clin. Infect. Dis.* **16:** 392–396.

Pachner, A. R. (1986). Spirochetal diseases of the CNS. *Neurol. Clin.* **4:** 207–222.

Pachner, A. R. (1989). Neurologic manifestations of Lyme disease, the new "great imitator." *Rev. Infect. Dis.* **11**(Suppl. 6)**:** s1482–s1486.

Pachner, A. R., Duray, P., and Steere, A. C. (1989). Central nervous system manifestations of Lyme disease. *Arch. Neurol.* **46:** 790–795.

Pachner, A. R., and Steere, A. C. (1984). Neurological findings of Lyme disease. *Yale J. Biol. Med.* **57:** 481–483.

Pachner, A. R., and Steere, A. C. (1985). The triad of neurologic manifestations of Lyme disease: Meningitis, cranial neuritis, and radiculoneuritis. *Neurology* **35:** 47–53.

Pass, H. L., Dattwyler, R., Ollo, C., and Mitchel, M. (1987). Nseuropsychological measures of a reversible dementia in Lyme disease. *J. Clin. Exp. Neuropsychol.* **9:** 75.

Piesman, J., Mather, T. N., Sinsky, R. J., and Spielman, A. (1987). Duration of tick attachment and *Borrelia burgdorferi* transmission. *J. Clin. Microbiol.* **25:** 557–558.

Piesman, J., Maupin, G. O., Campos, E. G., and Happ, C. M. (1991). Duration of adult female ixodes dammini attachment and transmission of *Borrelia burgdorferi* with description of needle aspiration isolation method. *J. Infect. Dis.* **163:** 895–897.

Pollina, D. A., Elkins, L. E., Squires, N. K., Scheffer, S. R., and Krupp, L. B. (1999). Does process-specific slowing account for cognitive deficits in Lyme disease? *Appl. Neuropsychol.* **6:** 27–32.

Pollina, D. A., Sliwinski, M., Squires, N. K., and Krupp, L. B. (1999). Cognitive processing speed in Lyme disease. *Neuropsychiatry Neuropsychol. Behav. Neurol.* **12:** 72–78.

Ravdin, L. D., Hilton, E., Primeau, M., Clements, C., and Barr, W. B. (1996). Memory functioning in Lyme borreliosis. *J. Clin. Psychiatry* **57:** 282–286.

Reik, L., Burgdorfer, W., and Donaldson, J. O. (1986). Neurologic abnormalities in Lyme disease without erythema chronicum migrans. *Am. J. Med.* **81:** 923–927.

Reik, L., Smith, L., Kahn, A., and Nelson, W. (1985). Demyelinating encephalopathy in Lyme disease. *Neurology* **35:** 267–269.

Roelcke, U., Barnett, W., Wilder-Smith, E., Sigmund, D., and Hacke, W. (1992). Untreated neuroborreliosis: Bannwarth's syndrome evolving into acute schizophrenia-like psychosis. *J. Neurol.* **239:** 129–131.

Rowe, P. M. (2000). Chronic Lyme disease: The debate goes on. *Lancet* **355:** 1436.

Schmutzhard, E., Pohl, P., Stockhammer, G., Kleedorfer, B., and Stanek, G. (1988). Unusual neurological manifestations of second-stage Lyme borreliosis. *Ann. N. Y. Acad. Sci.* **539:** 495–496.

Schwartz, B. S., Goldstein, M. D., Ribeiro, J. M. C., Schulze, T. L., and Shahied, S. I. (1989). Antibody testing in Lyme disease. *JAMA* **262:** 3431–3434.

Shadick, N. A., Phillips, C. B., Sangha, O., Logigian, E. L., Kaplan, R. F., Wright, E. A., et al. (1999). Musculoskeletal and neurologic outcomes in patients with previously treated Lyme disease. *Ann. Intern. Med.* **131:** 919–926.

Shadick, N. A., Phillips, C. B., Logigian, E. L., Steere, A. C., Kaplan, R. F., Berardi, V. P., et al. (1994). The long-term clinical outcome of Lyme disease. A population-based retrospective cohort study. *Ann. Intern. Med.* **121:** 560–567.

Sigal, L. H., and Williams, S. (1997). A monoclonal antibody to *Borrelia burgdorferi* flagellin modifies neuroblastoma cell neuritogenesis in vitro: A possible role for autoimmunity in the neuropathy of Lyme disease. *Infect. Immun.* **65:** 1722–1728.

Steere, A. C. (1989). Lyme disease. *N. Engl. J. Med.* **321:** 586–594.

Steere, A. C. (1997). Diagnosis and treatment of Lyme arthritis. *Med. Clin. North Am.* **81:** 179–194.

Steere, A. C. (2001). Lyme disease. *N. Engl. J. Med.* **345:** 115–125.

Steere, A. C., Bartenhagen, N. H., Craft, J. E., Hutchinson, G. J., Newman, J. H., Rahn, D. W., et al. (1983). The early clinical manifestations of Lyme disease. *Ann. Intern. Med.* **99:** 76–82.

Steere, A. C., Green, J., Schoen, R. T., Taylor, E., Hutchinson, G. J., Rahn, D. W., et al. (1985). Successful parenteral penicillin therapy of established Lyme arthritis. *N. Engl. J. Med.* **312:** 869–874.

Steere, A. C., Malawista, S. E., Bartenhagen, N. H., Spieler, P. N., Newman, J. H., Rahn, D. W., et al. (1984). The clinical spectrum and treatment of Lyme disease. *Yale J. Biol. Med.* **57:** 453–461.

Steere, A. C., Malawista, S. E., Snydman, D. R., Shope, R. E., Andiman, W. A., Ross, M. A., et al. (1977). Lyme arthritis: An epidemic of oligoarticular arthritis in children and adults in three Connecticut communities. *Rheumatism* **20:** 7–17. \

Steere, A. C., Taylor, E., McHugh, G. L., and Logigian, E. L. (1993). The overdiagnosis of Lyme disease. *JAMA* **269:** 1812–1816.

Steere, A. C., Taylor, E., Wilson, M. L., Levine, J. F., and Spielman, A. (1986). Longitudinal assessment of the clinical and epidemiological features of Lyme disease in a defined population. *J. Infect. Dis.* **154:** 295–300.

Svetina, C., Barr, W. B., Rastogi, R., and Hilton, E. (1999). The neuropsychological examination of naming in Lyme borreliosis. *Appl. Neuropsychol.* **6:** 33–38.

Treib, J., Grauer, M. T., Haass, A., Langenbach, J., Holzer, G., and Woessner, R. (2000). Chronic fatigue syndrome in patients with Lyme borreliosis. *Eur. Neurol.* **43:** 107–109.

Tremont, G., Halpert, S., Javorsky, D., and Stern, R. A. (2000). Differential impact of executive dysfunction on verbal list learning and story recall. *Clin. Neuropsychol.* **14:** 295–302.

Uldry, P. A., Regli, R., and Bobousslovsky, J. (1987). Cerebral angiopathy and recurrent strokes following *Borrelia burgdorferi* infection. *J. Neurol. Neurosurg. Psychiatry* **50:** 1703–1704.

Veendendall-Hilbers, J. A., Perquin, W. V. M., Hoogland, P. H., and Doornbos, L. (1988). Basal meningo-vasculitis and occlusion of the basilar artery in two cases of *Borrelia burgdorferi* infection. *Neurology* **38:** 1317–1319.

Wang, T. J., Liang, M. H., Sangha, O., Phillips, C. B., Lew, R. A., Wright, E. A., et al. (2000). Coexposure to *Borrelia burgdorferi* and babesia microti does not worsen the long-term outcome of Lyme disease. *Clin. Infect. Dis.* **31:** 1149–1154.

Weder, B., Wiedersheim, P., Matter, L., Steck, A., and Otto, F. (1987). Chronic progressive neurological involvement in *Borrelia burgdorferi* infection. *J. Neurol.* **234:** 40–43.

Westervelt, H. J., and McCaffrey, R. J. (1999). Neuropsychological functioning in chronic Lyme disease: The role of mental effort [Abstract]. *Arch. Clin. Neuropsychol.* **14:** 650–651.

White, D. J., Chang, H. G., Benach, J. L., Bosler, E. M., Meldrum, S. C., Means, R. G., et al. (1991). The geographical spread and temporal increase of the Lyme disease epidemic. *JAMA* **266:** 1230–1236.