COGNITIVE DYSFUNCTION IN SYSTEMIC LUPUS ERYTHEMATOSUS

DISSERTATION

Presented to the Graduate Council of the University of North Texas in Partial Fulfillment of the Requirements For the Degree of

DOCTOR OF PHILOSOPHY

By

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Denton, Texas
August, 1997

The purpose of the study was to determine the point prevalence of cognitive dysfunction in patients with systemic lupus erythematosus (SLE) and to investigate its association with corticosteroids and depression. The severity of dysfunction and the pattern of cognitive changes were examined. This study hypothesized that cognitive dysfunction is common in SLE and many previous studies have underestimated its prevalence, partially due to using limited neuropsychological batteries and insensitive test instruments. It was further hypothesized that the pattern of cognitive changes in SLE patients will resemble that observed in subcortical dementias. The association between cognitive impairment, duration of steroid use, depression, age, and education was examined by using standard multiple regression. Fifty subjects, recruited from the community, participated. Subjects were administered a comprehensive battery of neuropsychological tests. Self-report questionnaires were used to collect demographic data, medical history, and neurologic symptoms. The Beck
Depression Inventory (BDI) was used to assess depressive symptoms. Fatigue was evaluated with the Fatigue Severity Scale (FSS). The prevalence of cognitive impairment was 74%. Most subjects presented with mild, diffuse neurocognitive dysfunction that was consistent with a pattern often observed in subcortical dementias. Cognitive impairment was associated with somatic symptoms of depression and education. Age, fatigue, and duration of steroid use were not significant predictors of cognitive functioning.
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TABLE OF CONTENTS

LIST OF TABLES ......................................................... iv

Chapter

1. INTRODUCTION .................................................... 1
   Association with Psychological Distress
   Association with Disease Activity and Medication
   Nature of Cognitive Dysfunction
   Pattern of Cognitive Dysfunction
   Severity and Course of Cognitive Dysfunction
   Purpose and Hypotheses

2. METHOD .......................................................... 33
   Subjects
   Materials
   Procedure
   Data Analysis

3. RESULTS .......................................................... 44
   Descriptive Data
   Prevalence and Severity
   Pattern of Cognitive Dysfunction
   Role of Medications, Depression, and Fatigue

4. DISCUSSION ....................................................... 58

REFERENCES ......................................................... 72
<table>
<thead>
<tr>
<th>Table</th>
<th>Description</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>Demographic features of study population</td>
<td>44</td>
</tr>
<tr>
<td>2.</td>
<td>Self-reported cognitive difficulties</td>
<td>46</td>
</tr>
<tr>
<td>3.</td>
<td>Severity ratings of test protocols</td>
<td>47</td>
</tr>
<tr>
<td>4.</td>
<td>Neuropsychological test measures and proportion impaired</td>
<td>49</td>
</tr>
<tr>
<td>5.</td>
<td>Results of multiple regression</td>
<td>55</td>
</tr>
</tbody>
</table>
CHAPTER 1

INTRODUCTION

Neuropsychiatric systemic lupus erythematosus (NPSLE) is a general term used to describe a variety of neuropsychiatric manifestations including seizures, cerebrovascular accidents, psychosis, cranial and peripheral neuropathies, and transverse myelitis. It is reported to occur in 25%-75% of cases of systematic lupus erythematosus (SLE), (Kovacs, Murray, Urowitz, & Gladman, 1993). Organic brain syndromes and psychiatric disturbances are the most common presentations of NPSLE (West, 1994). The pathogenesis of NPSLE remains unclear. The proposed mechanisms include vasculopathy mediated by immune complexes and direct antibody-mediated neuronal dysfunction (Barr & Merchut, 1992).

Neuropsychological testing has not been used extensively in clinical practice or research to evaluate the nature and severity of cognitive dysfunction in SLE, although many SLE patients complain of memory, concentration, and word-finding difficulties. Significant cognitive dysfunction in SLE with or without the presence of overt central nervous system (CNS) involvement has been reported to occur in 17% to 66% of SLE patients (Hay, Black,
Huddy, Creed, Tomenson, Bernstein, & Holt, 1992; Carbotte, Denburg, & Denburg, 1986). Individuals with previous or current CNS involvement present with cognitive dysfunction at a high rate, with the prevalence estimates ranging up to 88% (Carbotte et al., 1986). SLE patients without documented current or past CNS involvement, also have a significantly higher prevalence of cognitive impairment (14% to 54%), than matched samples of healthy subjects or other patients with systemic disease (Koffler, 1987; Wekking, Nossent, van Dam, & Swaak, 1991). Routine, clinical exams are typically insensitive to subtle cognitive changes that can be detected by neuropsychological testing. Therefore, it is not surprising that CNS involvement had not been previously documented in these patients. It is also suspected that cognitive changes are under-reported by SLE patients, and often not formally evaluated.

The prevalence estimates are variable due to different patient samples, test protocol, and decision criteria used in the neuropsychological studies. Selection bias is evident as most of the studies have used clinic-attending samples. Furthermore, the prevalence estimates are based on samples that include widely divergent proportions of subjects with NPSLE. Higher prevalence rates for cognitive dysfunction would be expected to be obtained by studies with a large proportion NPSLE subjects, given that organic brain syndrome accounts for the majority of diagnoses of NPSLE.
Decision rules and control groups on which the decisions of impairment have been based have varied. Some studies have used normative data established for the individual tests, others have used normal control groups and/or rheumatoid arthritis (RA) patients. The control groups have been typically small in size and often not screened for neurological dysfunction. Perhaps the most serious shortcoming of many of the neuropsychological studies has been the use of very limited neuropsychological batteries and insensitive measures of neurocognitive functioning. Such studies typically yielded very low prevalence rates and possibly a high rate of false negatives. Studies that have used comprehensive neuropsychological batteries obtained prevalence estimates for cognitive dysfunction averaging around 50% (Carbotte et al., 1986; Wekking et al. 1991; Koffler, 1987).

There is considerable diversity in the kinds of cognitive impairment shown by SLE patients and, as of yet, no clear pattern has emerged. This may be due to the methodological differences and/or shortcomings of the studies or may represent the heterogeneity in the clinical presentation of CNS involvement. Cognitive deficits identified include changes in memory, attention, concentration, visuospatial skills, verbal fluency and cognitive flexibility.
The severity of cognitive dysfunction among SLE patients is unclear due to the variability in the decision criteria as to what constitutes a significant impairment. The incidence of dementia among SLE patients is unknown.

A number factors may account for or contribute to the finding of cognitive impairment in SLE including emotional disturbance, disease activity and severity, and medication, particularly corticosteroids. The evidence regarding the association of these variables to cognitive dysfunction is limited and inconsistent.

The following sections will review the literature on neurocognitive functioning in SLE and associated variables.

Association between Cognitive Impairment and Psychological Distress

Most studies have not found a significant relationship between cognitive dysfunction and emotional disturbance (Denburg, Carbotte, & Denburg, 1987; Gingsburg, Wright, Larson, Fossel, Albert, Schur, & Liang, 1992; Kerr, Edworthy, Samuels, & Violato, 1994). However, there is some indication that they may co-occur, especially in NPSLE patients. Furthermore, psychiatric disturbances may be associated with specific neurocognitive deficits.

Carbotte et al. (1986), found that patients with NPSLE were more distressed psychologically than rheumatoid arthritis (RA) patients and normal controls as measured by the Minnesota Multiphasic Personality Inventory (MMPI).
Significant association between psychological distress and cognitive impairment was found, with 55% of the SLE sample presenting with both cognitive impairment and psychological distress. However, 45% of the sample was either impaired or distressed, but not both. Reanalysis of the data with 14 additional subjects (70 total) yielded no significant association with psychological distress and cognitive impairment within the total SLE patient sample (Denburg et al., 1987). However, psychological distress was found to be associated with decreased short-term memory and verbal fluency for cognitively impaired NPSLE patients. Hay et al. (1992) also showed that psychiatric disturbance as assessed by a structured psychiatric interview was associated with decreased verbal fluency and short-term visual memory, but no association between a psychiatric disorder, systemic disease activity or CNS involvement was found.

NPSLE subjects were found to be more psychologically disturbed than RA subjects as measured by the Millon Multiaxial Inventory (MCMI) in the Wekking et al. (1991) study. The non-NPSLE subjects did not significantly differ from RA or the NPSLE subjects, and the pattern of scale elevations was similar among all three groups. These investigators found high prevalence rates of cognitive dysfunction for all groups, with 55% of the NPSLE, 54% of
the non-NPSLE, and 40% of the RA subjects presenting with cognitive dysfunction. However, the study did not examine the relationship with emotional distress.

The use of instruments such as the MMPI or the MCMI may be inappropriate in assessing emotional dysfunction in SLE as they are not standardized for a medical population. SLE patients may obtain significant elevations on some of the scales by simply endorsing the physical symptoms of the disorder, thus any correlation found between emotional disturbance and cognitive dysfunction may be confounded by physical symptoms. Furthermore, the studies that found an association with specific cognitive deficits did not differentiate between the types of psychiatric disturbances. In the Hay et al. (1992) study, the SLE patients received a variety of psychiatric diagnoses. In the Carbotte et al. (1987) study, emotional distress was defined as two or more scale elevations on the MMPI (excluding scales 5 and 0). These results suggest that any type of psychological dysfunction may be associated with impaired memory and verbal fluency, which is questionable. If an association exists between emotional disturbance and cognitive dysfunction the most likely contributing factors are depression and anxiety which often have an adverse effect on neuropsychological test performance.

Depression is the most commonly reported psychiatric symptom in SLE, presented by approximately 40% of patients
(Wekking, 1993; Lim, Ron & Ormedoc, 1988). There is some evidence of an organic basis for depression in SLE, as depression has been found to correlate highly with documented CNS involvement, but not with any other disease manifestations (Utset, Golden, Siberry, Kiri, Crum & Petri, 1994). Anxiety disorders, panic disorders, and phobias are also relatively common. One study reported a prevalence rate of 56% for phobia (Lindal, Thorlacius, Steinsson & Stefansson, 1995). Shortall, Isenberg and Newman (1995) found that mood disorders were unrelated to disease activity and neurocognitive test performance, but were associated with subjective ratings of cognition, self-esteem, and social factors.

Other psychiatric symptoms occur less frequently, with approximately 5%-13% presenting with schizophreniform or paranoid psychosis (Lim et al., 1988; Shapiro, 1993). The psychotic episodes are typically short-lived and often respond to steroid treatment. Steroid-induced psychosis has also been documented in SLE, but occurs in less than 5% of cases (Shapiro, 1993). Manic episodes, personality changes, mood swings, anxiety, and neurosis also occur, and are subject to ongoing debate as to whether they have an organic basis, are premorbid characteristics, or reactions to the disorder. Psychosis in SLE is generally thought to have a neurologic basis (Wekking, 1993).
The most consistent findings from the studies reviewed are that psychiatric morbidity in SLE is greater than that found in the general population, and NPSLE patients present with more severe psychopathology than the overall SLE population. It is hardly surprising that NPSLE patients as a group present with more psychopathology given that the presence of a psychiatric disturbance is one of the most common criteria used to diagnose NPSLE.

It is unclear whether SLE patients present with more psychopathology than other chronic illness populations, as the studies have yielded mixed results. Psychiatric morbidity in RA has been consistently found to be very similar to that presented by SLE patients as concluded by Wekking (1993) in a review of 21 studies on psychiatric symptoms in SLE. There appears to be striking similarities between multiple sclerosis (MS) and SLE patients with respect to prevalence and type of psychiatric symptoms (Minden & Schiffer, 1990; Rao, Huber, & Bornstein, 1992), which suggest that psychiatric symptoms may be general symptoms associated with autoimmune disorders. It appears unlikely that emotional distress, by itself, would result in significant cognitive impairment, but depression may be exacerbating existing deficits. It is also conceivable that those patients with more severe cognitive dysfunction would present with greater emotional distress as a reaction to their limitations. However, the relationship may not be
causal, and the two may co-occur as independent manifestations of a compromised neural substrate.

**Association between Cognitive Impairment, Disease Activity and Medication**

Several studies have failed to find an association between generalized disease activity and overall cognitive impairment (Carbotte, Denburg & Long, 1987; Hay et al., 1992; Gingsburg, Wright & Larson, Fossel, Albert, Schur, & Liang, 1992; Kerr, Edworthy, Samuels, & Violato, 1994). However, one series of studies reported increased disease activity to be associated with impaired immediate memory and concentration (Fisk, Eastwood, Sherwood, & Hanley, 1993; Hanley et al., 1992). No significant associations have been found between currently active individual organ system involvement (i.e., renal vs. skin and joint involvement) and cognitive impairment (Hanly et al., 1992). The lack of association between cognitive dysfunction and disease activity or severity may be because some SLE patients present with residual cognitive dysfunction due to prior CNS events.

Evidence regarding the association between steroid use and cognitive impairment is inconsistent. A number of studies have suggested that corticosteroid use is not associated with cognitive impairment (Carbotte et al., 1986; Hay et al., 1992; Gingsburg et al., 1992; Kerr et al., 1994), but other studies indicate that a relationship
exists. Hanly et al. (1991) found that corticosteroid use at the time of the assessment was more common in patients with cognitive impairment, however, re-analysis of data by Fisk et al. (1993), revealed no significant differences between cognitively intact and impaired patients when disease activity was considered as a covered in the analysis. Ferstl, Nieman, Biehl, Hinrichsen, & Kirch, (1992) reported that SLE patients did not differ from the corticosteroid-treated patients on any of the neuropsychological measures, with both groups demonstrating impairment in short-term memory and reaction time as compared to normal controls. However, the sample size was small with 15 SALE patients, 15 normal controls, and 8 patients on corticosteroids. Furthermore, the corticosteroid group was unselected with respect to diagnosis and not screened for neurological dysfunction.

A recent study on the effects of chronic Prednisone treatment on memory with patients with systemic diseases indicated that patients receiving steroids for at least 1 year performed significantly worse than medical controls on explicit memory as measured with the Logical Memory and the California Verbal Learning tests (Keenan, Jacobson, Soleymani, Mayes, Stress, & Yaldoo, 1996). Elderly patients were found to be more susceptible to memory impairment following steroid treatment. Furthermore, the findings of a separate prospective study indicated that even acute
treatment can affect explicit memory functioning. Most of the subjects in this study had rheumatoid arthritis and no patients with SLE were included.

All the reviewed studies in SLE examined the concurrent use of corticosteroids, and ignored the dosage and duration of use. The role of corticosteroids in cognitive impairment is of critical importance because they are the mainstay for treatment of active SLE. Affective and cognitive side-effects of exogenous corticosteroids are well known, and appear to be dose dependent. High doses (above 40 mg) have been reported to be associated with psychosis, anxiety, depression, hypomania, and subjective complaints of distractibility and memory impairment (Hall, Popkin, Stickney, 1979). Chronic use of corticosteroids has also been found to produce cortical atrophy (Wolkowitz & Reus, 1990). Pathological and diagnostic studies have revealed cortical atrophy in SLE patients which may account for the cognitive deficits seen (Ostrov, Quencer, Gaylis, Altman, 1982; Kaell, Shetty, Lee, Lockshin. 1986). However, improvement in cognitive functioning following corticosteroid therapy has also been reported (Denburg, Carbotte, & Denburg, 1987, 1994; Bell, Partington, Robbins, Graziano, Turski, & Kornguth, 1991). SLE patients take a variety of other medications, i.e., nonsteroidal anti-inflammatory drugs, antimalarials, and other immunosuppressives, some of which are neurotoxic, and can
have affective and cognitive side-effects. Their effects have not been examined in any of the neuropsychologic studies reviewed.

Fatigue is a common complaint among SLE patients (Krupp, LaRocca, Muir-Nash & Steinberg, 1989), and it is known to affect cognitive test performance, yet no studies were found that examined this relationship. In the present study the effects of subjective ratings of fatigue on neuropsychological test performance and duration of steroid use were examined.

Nature of Cognitive Dysfunction in SLE

Carbotte et al. (1986) were the first investigators to use neuropsychological tests to assess the patterns and prevalence of cognitive deficits in SLE. A comprehensive battery of neuropsychological tests was administered to 62 female SLE patients, 12 patients with rheumatoid arthritis, and 35 normal control subjects. An overall prevalence of cognitive impairment of 66% was obtained for the SLE patient sample. The proportion of impaired patients with past NPSLE symptomatology and those with current NPSLE symptoms was very high (87% and 81%, respectively). Furthermore, a significant percentage of patients (42%) with no previous or current documented neuropsychiatric symptomatology presented with cognitive impairment. Patients with active or inactive NPSLE as a group differed from controls on measures of thematic and visuospatial memory, reasoning, and fluency in
both verbal and nonverbal modalities. Patients with no present or past history of NPSLE differed as a group from controls on a measure of visual-spatial/motor fluency.

Koffler (1987) also found a high incidence of cognitive impairment (87.5%) among SLE patients with symptoms of CNS involvement using the Luria-Nebraska neuropsychological battery. In the non-NPSLE group, 14% were identified as cognitively impaired. Prevalence of cognitive impairment for the total SLE group was 40%. Four clinical scales (visual, arithmetic, writing, intelligence) showed consistent abnormalities.

Wekking et al. (1991), reported that 55% of NPSLE patients, and 40% of non-NPSLE patients demonstrated markedly impaired performance (defined as 3 or more deficient scores) on a comprehensive neuropsychological battery. They also found that 40% of RA patients used as a comparison group demonstrated marked cognitive impairment. As a group the SLE patients performed worse than the RA patients on speed and flexibility in information processing. The study had a relatively small sample size (20 SLE and 20 RA patients), and standard deviations for the NPSLE group were very high, exceeding the mean for some of the tests, which could have prevented finding statistically significant differences between the groups.

In contrast to the above findings another series of studies (Hanley et al., 1992; Fisk et al., 1993) identified
only 21% of SLE subjects as cognitively impaired. Cognitive impairment with active NPSLE was more common (40%), compared to patients with inactive NPSLE (20%) or those without known clinical NPSLE (20%). The battery consisted of selected subtests from the Wechsler Adult Intelligence Test-Revised (WAIS-R) and the Wechsler Memory Scale-Revised (WMS-R), and the North American Reading Test (NART). The limited test battery and the small number of active NPSLE patients (7%) included in the sample may account for the obtained low prevalence rate. Significant deficits were identified in the areas of memory retrieval, visual construction, attention/concentration, and psychomotor speed according to normative data for the tests. Both RA and normal controls were used, however, no data were presented comparing the neurocognitive test performances of the three groups.

Similar prevalence estimates of 26% were obtained by Hay et al. (1992). The neuropsychological test battery consisted of selected tests from the WAIS-R, NART, the Verbal Fluency Test and the Benton Visual Retention Test, Part A. Cognitive impairment (defined as defective performance on 2 or more tests) was identified in 62% of patients with CNS involvement, and in 17% of those with no overt evidence of CNS involvement. More than 50% of the SLE patients performed in the impaired range on the verbal fluency and visual memory measures according to published normative data. No control group was used.
Gingsburg et al. (1992) used RA patients as controls and reported that SLE patients had a poorer performance than RA patients on a test of complex attention and tests of visuospatial ability. The prevalence or severity of cognitive dysfunction was not reported. Neither normative data nor normal controls were used.

Reduced attentional capacity with complex stimuli in SLE patients was also reported by Kerr, Edworthy, Samuels & Violato (1994) as compared to normal controls, however, no differences between RA and SLE subjects were found.

Deficits in short-term memory and reaction time were demonstrated by SLE subjects as compared to normal controls in the Ferstl et al. (1992) study, but they did not differ significantly on any of the measures from the corticosteroid treated group. As already discussed the corticosteroid group was small (8) and unselected for neurologic or psychiatric disorders.

Impairment in visual and verbal short-term memory as well as visual-perceptual deficits were reported by Kutner, Busch, Mahmood, Racis, and Krey (1988) as compared to RA patients. However, significant differences in cognitive functioning were found on more than half of the tests between RA patients and normal controls.

The above represents the bulk of neuropsychological studies in SLE. A number of problems with these studies can be identified. Several of the studies used RA patients as a
comparison group, and perhaps the most consistent finding from these studies is that cognitive functioning of RA patients is worse than that of normal controls. The prevalence of significant cognitive impairment in RA patients ranges up to 40% (Wekking et al., 1991), which exceeds the prevalence estimates obtained for SLE patients in some of the studies. RA patients also present with similar psychiatric morbidity, as previously discussed. This suggests that emotional and cognitive dysfunction may be general symptoms associated with autoimmune disorders. Whether the dysfunction results from the same pathogenic mechanisms, medication side-effects, the presence of a chronic, often debilitating illness, or is due to some other disease variables underlying both disorders are questions yet to be answered. However, it is clear that RA patients are an inappropriate comparison group when attempting to establish the prevalence and nature of cognitive dysfunction in SLE, particularly when used alone without normal controls or reference to normative data.

Sample sizes were small in some of the studies, decreasing the generalizability and compromising the reliability of the findings. Parametric statistics were used inappropriately by some of the studies to analyze obviously skewed data, as evidenced by very high standard deviations. However, the most frequent limitation was the use of a small control sample which in most studies was less
than half of the number of SLE subjects included. This is particularly problematic for the studies which established the presence or absence of cognitive dysfunction based on the performance of a small control sample, often selected without respect to neurological or psychiatric disturbance. Most of the studies reviewed appeared to have used no inclusion/exclusion criteria for participation other than the diagnosis of SLE, which may account for the inconsistent findings.

Selection bias, perhaps unavoidable, is present in all of the studies since volunteers were used. However, most of the studies used clinic-attending samples introducing an additional bias. Criteria for classifying individuals as either cognitively impaired or non-impaired varied from study to study, and were sometimes questionable.

Many of the studies used limited neuropsychological batteries. These studies yielded low prevalence estimates and possibly a high rate of false negatives. Furthermore, due to the methodological problems in the studies, any results regarding the association of disease activity, medication or emotional functioning become questionable. A large battery of neuropsychological tests may not be necessary for detecting the existence of cognitive impairment in SLE; but if the establishment of prevalence and nature of cognitive impairment is proposed, the use of a comprehensive battery which includes tests sensitive to
subtle neurocognitive dysfunction would seem advisable, given the heterogeneity of the disease and the proposed pathogenic mechanisms.

**Patterns of Cognitive Dysfunction in SLE**

There appears to be considerable diversity of neurocognitive dysfunction in SLE, and no patterns have been identified. This may represent the heterogeneity in the clinical presentation of CNS involvement or may be due to the methodological differences and/or short-comings of the studies which make interpretation of the results and comparisons between studies difficult. However, when the findings of all the neuropsychological studies are summarized, some consistent deficits can be found that suggest a pattern. Impaired visual and verbal short-term memory has been reported by most of the studies (Hanley et al., 1992; Hay et al., 1992; Ferstl et al., 1992; Carbotte et al., 1986; Gingsburg et al., 1992; Kutner et al., 1994). Immediate and delayed recall is reported to be impaired in most studies. In the Hanley et al. (1992) study 87% of subjects demonstrated deficits in memory retrieval, and 27% with recall on the California Verbal Learning Test.

Decreased verbal fluency was found by all studies that assessed it (Hay et al., 1992; Carbotte et al. 1986; Denburg et al., 1987). Impaired visuospatial functioning was reported by several studies (Gingsburg et al., 1992; Hanley et al., 1991; Denburg et al., 1987; Kutner et al., 1988), as
well as decreased cognitive flexibility (Wekking et al., 1991; Denburg et al., 1987). Various other deficits have been found on tests that measure reaction time (Ferstl et al., 1992), attention and concentration (Hanly et al., 1991; Kerr et al., 1994; Ginsburg et al., 1992) and psychomotor speed (Hanly et al., 1991; Denburg et al., 1987).

Overall, patients with SLE appear consistently to do more poorly than controls on most timed tests regardless of what function the test measures or the mode of response, which suggests a general slowing of information processing. There does not appear to be a general decline of intellectual abilities as measured by the WAIS or WAIS-R, although one study found decreased Performance IQ in all SLE patients as compared to normal controls (Denburg et al., 1987). It should be noted that most of the subtests on the Performance scale are timed. Language abilities also appear intact, although not formally evaluated in any of the studies. This pattern of deficits closely resembles the pattern of deficits observed in subcortical dementias.

Slowed information processing is a cardinal feature of subcortical dementia (Huber & Shuttleworth, 1989; Mahler & Benson, 1991). Memory retrieval is typically impaired, but recognition memory is intact. Memory deficits are generally milder than those observed in cortical dementias such as Alzheimers. Impairment on tasks of executive function that involve concept formation and cognitive flexibility has been
shown consistently with the subcortical syndrome. Verbal fluency and visuospatial skills are often impaired. Movement disorders (i.e. the chorea of HD and rigidity and bradykinesis of PD) are common (Cummings & Benson, 1990). General intellectual decline is usually not observed as measured by standardized intelligence tests, although some studies have shown decreased Performance IQ as measured by the Wechsler scales due to poor performance on the timed performance tests (Cummings, Benson, and LoVerme, 1980). Cortical dementias tend to be more severe overall and typically include symptoms such as aphasia, agnosia, and apraxia, which are usually absent in subcortical syndromes. However, impairment on motoric speech functions, such as dysarthria, decreased phrase length, and reduced control over rate and intensity of delivery are associated with subcortical dementias. Impaired writing mechanics, such as tremor, cramped appearance, and micrographia are also observed (Cummings, 1990).

Depression and apathy are common in subcortical syndromes. Personality changes, irritability, and emotional lability are often presented. Schizophrenic-like symptoms are seen infrequently, but occur in some subcortical syndromes (Mahler et al., 1991).

Subcortical dementia has been identified in Parkinsons disease (PD), Huntington's disease (HD), vascular dementias, progressive supranuclear palsy, multiple sclerosis (MS), and
the acquired immune deficiency syndrome (AIDS) dementia complex among others (Cummings, 1990).

The pattern of cognitive deficits shown by SLE patients, i.e., slowed information processing and psychomotor speed, impaired attention and concentration, cognitive inflexibility, short-term memory deficits, decreased verbal fluency and visuospatial skills, resembles the pattern identified in other autoimmune disorders such as MS (Rao, Leo, Bernadin, Unverzagt, 1991), and HIV (Van Gorp, Mitrushina, Cummings, Satz, & Modesitt, 1989), as well as other disorders with definite subcortical involvement such as HD and PD (Cummings and Benson, 1984).

None of the neuropsychological studies reviewed reported symptoms of agnosia, apraxia, or aphasia in SLE patients. However, such symptoms may occur in individual patients, possibly due to focal cortical lesions. Movement disorders occur in SLE, but in less than 5% of cases (Barr & Merchut, 1992). Chorea is the most common presentation, but cerebellar ataxia, hemiballismus, and Parkinson's-like rigidity and tremor have also been reported. Focal subcortical grey matter lesions are usually found in SLE patients with movement disorders (West, 1994).

The type and prevalence of psychiatric disorders in SLE appears very similar to those found in subcortical syndromes. Depression is the most frequent symptom, followed by schizophrenic-like symptoms, apathy, manic episodes and
personality changes, which occur at a higher rate than in the general population and often in individuals without premorbid history of psychiatric disorders.

Subcortical dementias have pathologic changes located primarily in the white matter and deep structures such as basal ganglia, thalamus, and brain stem, with relative sparing of the cortex. However, cortical degeneration is also present in PD (Lishman, 1978), and significant atrophy of the frontal cortex and the corpus callosum has been shown in HD (Lishman, 1978). Cerebral atrophy occurs in MS (Huber, 1987) and in AIDS (Navia, Cho, Petito, & Pierce, 1986), although most of the pathology involves the white matter and subcortical structures.

Diagnostic studies using magnetic resonance imaging (MRI) with NPSLE patients have most commonly shown small and/or large, often multiple, high-signal intensity lesions predominately in the subcortical and deep white matter and hyperintensity bordering the lateral ventricles (Bell, Partington, Robbins, Graziano, Turski, & Kornguth, 1991; Jarek, West, Baker, & Rak, 1994; Molad, Yechezkel, Sidi, Gornish, Lerner, Pinkhas & Weinberger, 1992; McCune, MacGuire, Aisen, & Gebarski, 1988). A recent study using CT scans with NPSLE patients found that 41% had normal scans, 30% had intracerebral calcification, with the globus pallidus involved in all. Putamen, thalamus, centrum venosum, basal ganglia, and cerebellum were involved with
varying degrees of frequency. The remaining patients presented with cerebral atrophy and/or infarcts (Raymond, Zariah, Samad, Chin, & Kong, 1996). Calcification of basal ganglia has also been found in other studies, but the most frequent findings using CT scans have been cortical atrophy and micro-infarcts involving both subcortical and cortical structures (Henle, Noreen, Walsh, & Sangalang, 1991; Kaell et al., 1986; Futrell, Schultz, Millikan, 1992). Patients with focal manifestations such as cerebrovascular accidents, cranial neuropathies, and focal seizures typically present with both subcortical and cortical grey matter lesions; however, the focal lesions are usually accompanied by diffuse white matter changes (Bell et al., 1991; McCune et al., 1988; West, 1994; Lim et al., 1988).

There is a paucity of studies that have attempted to correlate structural abnormalities as documented by brain imaging/scanning to cognitive dysfunction in SLE. Kutner et al. (1988) found abnormalities using CT scanning in 5/7 subjects identified as cognitively impaired using the Halstead-Reitan Neuropsychological Battery. Cortical atrophy was found in 4 patients and multiple infarcts in a fifth patient. Lim et al. (1988) reported no correlation between MRI findings and cognitive dysfunction as measured by the Mini Mental State Exam. None of the 40 subjects were found to be cognitively impaired, although multiple and significant MRI abnormalities were identified in 7/15
subjects, and some of the subjects presented with neurological symptoms such as hemiparesis. These two studies illustrate the importance of selecting measures that are sensitive to the type of lesions and cognitive deficits SLE patients present if any correlations are to be found. CT scans can be insensitive in detecting lesions in NPSLE. West (1994) reported that between 25%-80% of NPSLE patients with normal CT scans have abnormal MR cranial images. The Mini Mental State Exam and the Halstead-Reitan Battery may be inappropriate measures of neurocognitive functioning in SLE.

A few case studies have appeared in the literature recently using Positron Emission Tomography (PET) (Carbotte, Denburg, Denburg, Nahmias, & Garnett, 1992; Silverman, Zeit, Peyer, Gallegari, Alavi, & Von Feldt, 1994), but have mostly involved subjects with CVA's, symptoms of mania, psychosis or dementia. Patients with wide-spread PET abnormalities tend to have global impairments in cognition, depression and psychosis. Carbotte et al. (1992) reported reversible glucose hypometabolism in some patients with cognitive deficits following corticosteroid treatment.

The pathogenesis of NPSLE is unknown. The proposed mechanisms include vasculopathy mediated by immune complexes and/or direct antibody-mediated neuronal dysfunction (Barr & Merchut, 1992). The white matter lesions seen in brain scans are thought to represent demyelination, gliosis, and increased interstitial edema from focal ischemia or lacunar
infarctions (Jarek et al., 1994). The micro-infarcts occur at the arteriolar or capillary level, and it is uncertain if these vascular lesions are directly responsible for the behavioral manifestations of NPSLE or if they enhance the blood-brain barrier permeability which facilitates the access of pathogenic autoantibodies into CNS. A variety of brain cross-reactive autoantibodies have been implicated in the pathogenesis of NPSLE. Anti-phospholipid antibodies have been associated with focal neurologic disorders of vascular origin such as CVA, transverse myelitis, and chorea (Bell et al., 1991; Kovacs et al., 1993). Anti-ribosomal P protein antibodies occur more frequently in SLE patients with psychosis (Bonfa & Elkon, 1993). Anti-neuronal antibodies and lymphocytotoxic antibodies have been found to be associated with cognitive impairment in several studies (Denburg, Carbotte, & Denburg, 1987; Denburg, Behmann, Carbotte, & Denburg, 1993; Long, Denburg, Carbotte, Singal, & Denburg, 1990). Others have found no association between these antibodies and cognitive dysfunction (Hanly et al., 1993).

Whether the cognitive dysfunction in SLE is due to autoantibody mediated neuronal dysfunction or is primarily vascular in origin does not have much bearing on the pattern of neurocognitive changes seen. The subcortical dementia pattern has been identified in vascular disorders e.g.,Binswanger's disease, as well as in demyelinating diseases
e.g., AIDS encephalopathy and MS.

There appears to be substantial similarities between AIDS, MS, and SLE patients in terms of brain pathology and behavioral manifestations, although the three disorders are quite different in terms of etiology. If AIDS and MS are accepted as models of subcortical dementia in white matter diseases, the cognitive dysfunction in SLE could be anticipated to follow a similar pattern. It is further speculated that subcortical dementia may characterize cognitive dysfunction in most autoimmune disorders with CNS involvement.

The subcortical-cortical distinction in dementias is controversial, but clinically they appear to be distinct syndromes (Huber et al., 1986; Cummings et al., 1990; Pillon, Dubois, Polska, Agid, 1991). Objections to the distinction include the fact that cortical and subcortical structures can be involved in both types of dementia, and there is considerable overlap in cognitive deficits between the two dementia groups (Mayeux, Stern, Rosen & Benson, 1983). There are also significant differences in cognitive functioning between different subcortical syndromes, although the overall patterns are similar (Pillon et al. 1991).

There are a number of factors that contribute to the controversy including the insensitivity of many neuropsychological instruments to detect subcortical-type
deficits, and their inability to discriminate between the
two dementia groups, simply because they were not designed
to do so. The two dementia groups may perform equally poorly
on a particular neuropsychological measure, but for
different reasons. Slowed information processing, for
example, may affect performance on any timed test,
regardless of what function the test is designed to measure.

The term "subcortical dementia" has been criticized,
because many diseases producing the syndrome have
pathological changes that extend beyond the subcortical
regions and involve the cerebral cortex. However,
subcortical dementia is a clinical distinction rather than
an anatomic one. Frontal lobe-type deficits are commonly
seen in subcortical syndromes, due to extensive connections
between the frontal lobes and subcortical structures. The
symptoms may also be caused by disruption of the connections
between cortical and subcortical structures, as it appears
to be the case in AIDS and MS, where the lesions are
primarily in the subcortical white matter. Alternate,
perhaps more accurate, terms to subcortical dementia include
axial dementia and frontal-subcortical dementia.

Albert (1978) provides a conceptual framework for
differentiating cortical and subcortical dementias by
dividing neuropsychological activities into instrumental
and fundamental functions. Instrumental functions which
include language skills, perception and praxis are affected
by cortical degeneration. In contrast, subcortical dementias involve fundamental functions, such as arousal, attention, concentration, processing speed, motivation and mood.

The pattern of neuropsychological deficits and the type of psychiatric disturbances found in SLE patients resembles the profile of dysfunction observed in subcortical dementias. It is suggested that the fundamental functions are disrupted in SLE, but frontal dysfunction including difficulties with executive functioning, cognitive flexibility, and verbal fluency are also seen, possibly due to interruption of frontal/subcortical pathways.

An alternative hypothesis to subcortical dementia is the possibility that cerebral atrophy or diffuse CNS disturbance, structural and/or functional, produce the pattern of neuropsychological changes observed. There is no conclusive evidence, at the present time, to dispute this hypothesis in SLE, and even if the results of the proposed study show a predominately subcortical dementia pattern, it may remain a viable alternative explanation.

**Severity and Course of Cognitive Dysfunction in SLE**

Most of the studies reviewed have addressed severity of cognitive dysfunction in terms of a number of tests performed in the impaired range which may or may not be an accurate indication of severity of dysfunction, while some have not addressed it at all. There is also variability in
the decision criteria as to what constitutes a significant impairment. No studies have addressed the incidence of dementia among SLE patients according to the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) criteria or any other criteria. Cummings and Benson (1983) define dementia as an acquired and persistent impairment of the intellect with deficits at least in three of the following five areas: memory, visuospatial skills, emotional or personality change, cognition (i.e., concept formation, abstraction, calculations, judgement) and language. These criteria are similar to those used in the DSM-IV, but minimize the subjective judgement involved in determining the loss of social or occupational function as required by the DSM-IV criteria. The present study will use the Cummings and Benson (1983) criteria to determine the incidence of dementia, as it allows for interpretation of neuropsychological data in a more straightforward manner. Significant impairment on a neuropsychological measure is defined as two or more standard deviations below mean normal control performance. If three or more significant impairments are noted, the criteria for dementia are met.

There is a paucity of information about the clinical course of cognitive impairment including whether it remits, fluctuates or progressively worsens. One recent study suggested that cognitive impairment may fluctuate and even resolve without specific therapeutic interventions (Hanly,
Fisk, Sherwood, & Eastwood, 1994). Diagnostic studies using serial MRI scans have found that some MRI abnormalities (white matter lesions) are reversible after steroid treatment in SLE patients with diffuse CNS involvement (Bell et al., 1991; Sibbitt, Sibbitt, & Griffey, 1989). Improvement in cognition and mood was reported by Denburg et al., (1993) followed by a short-term low dose corticosteroid treatment in a single case, double-blind, controlled trial.

The findings of these studies suggest that cognitive dysfunction may fluctuate, and in some cases may be a transient phenomenon, perhaps due to an inflammatory process that is self-limiting or responds to steroids. However, group studies have consistently shown that cognitive test performance of individuals with a past history of CNS involvement is not significantly different from those with current CNS dysfunction, indicating residual neurologic impairment (Denburg et al., 1987; Hanley et al., 1992; Fisk et al., 1993).

It is not known whether the cognitive deficits occur early or late in the disease process. Studies with MS and AIDS patients indicate that cognitive deficits may be the first symptoms of the disorder, and occur without any other symptoms or neurologic signs. Psychiatric disturbance in SLE tends to occur early in the disease process (Wekking, 1991). Longitudinal studies are needed to address the
course of cognitive dysfunction and its prognostic implications.

**Purpose and Hypotheses**

The purpose of the study was to determine the point prevalence of cognitive impairment in self-selected, community residing, ambulatory patients with SLE using a comprehensive battery of neuropsychological tests. The severity of cognitive dysfunction and the pattern were examined, as well as the association with depression, fatigue and corticosteroid use. The study attempted to refine and extend previous investigations in order to clarify the nature and extent of neuropsychological impairment in SLE, and the association with possible confounding variables.

The following hypotheses were tested:

1. The prevalence of cognitive dysfunction in SLE exceeds 20%, when a comprehensive battery and an adequate sample size is used.

2. The pattern of deficits will resemble the pattern observed in subcortical dementia, as defined by the following: (a) slowed information processing; (b) disturbances of attention and concentration; (c) executive dysfunction including cognitive inflexibility and impaired concept formation; (d) memory dysfunction; (e) mood disturbance; (f) absence of aphasia, agnosia, and apraxia.

3. Exploratory analyses will be conducted to
determine the degree of association between cognitive impairment and fatigue, depression, and steroid use.
CHAPTER 2

METHOD

Subjects

Subjects were 50 patients with SLE, 18-60 years of age who fulfilled the diagnostic criteria for SLE established by the American College of Rheumatology (ACR). Individuals older than 60 years of age were not be included, because of well known effects of age on neurocognitive functioning. Furthermore, the subcortical dementia pattern has been suggested to characterize age-related cognitive changes (Van Gorp, Mitrushina, Cummings, Satz, Modesitt, 1989).

Volunteers from the UNT Health Science Center, support groups, and the community were recruited. Twenty-two of the subjects were patients of Raymond Pertusi, D.O., one of the principal investigators. Thirty-six of his patients were contacted, but 12 refused to participate. These patients' medical records were reviewed by Dr. Pertusi to ensure that subjects met the inclusion criteria. Additionally, 426 letters of request for participation were sent to the members of the North Texas Chapter of the Lupus Foundation. Thirty-six individuals responded, but only 19 met the inclusion criteria. The other 9 subjects were recruited from support groups and the community. All subjects, who were not
patients of Dr. Pertusi, were required to submit documentation from their physicians that they meet the ACR criteria for SLE. Subjects were excluded if they had a history of alcohol/drug abuse or nervous system disorder other than SLE, or a prior history of neurologic disease, seizure disorder, learning disability, head trauma, or psychiatric hospitalizations. Subjects whose primary language was not English and those involved in litigation were also excluded. Potential subjects were screened over the phone to determine if they met the inclusion criteria.

Materials

A questionnaire was used to collect the following information: occupation, employment status, education, duration of illness, time since diagnosis, medication use related to SLE, as well as any other medication use after completion of the neuropsychological testing. The subjects also completed the Neuropsychological Symptom Checklist, a self-report instrument of subjective complaints of neurologic dysfunction, the Fatigue Severity Scale (FSS; Krupp, Larocca, Muir-Nash, & Steinberg, 1989) and the Beck Depression Inventory (BDI; Beck, 1978). The FSS is a nine item self-report measure which assesses the effects of fatigue on daily living. The BDI is a 21-item self-report questionnaire which provides a quantitative assessment of the severity of depression. This test has not been standarized on medical populations, but was selected because
it allows for analysis of results with the exclusion of somatic symptoms.

In the selection of the tests for the neuropsychological battery several concerns were taken into account. All the tests selected have adequate normative data available, and have demonstrated reliability and validity in clinical and experimental use. The main consideration was that the battery survey all major areas of cognitive functioning and can be completed within a 2-hour time limit. The battery measured six broad areas of function: (1) abstract/conceptual reasoning; (2) attention and concentration; (3) memory; (4) visuospatial; (5) language; (6) praxis.

The tests were as follows:

1. Abstract/Conceptual Reasoning

BOOKLET CATEGORY TEST (Halstead-Reitan Neuropsychological Test Battery, HRNTB, 1979): a measure of abstraction, reasoning and logical analysis abilities. The subject is presented with a variety of stimulus figures varying in shape, number, size, location, and color, and the subject's task is to determine how these figures can be grouped by using abstract principles. The test is very sensitive to cerebral damage, but non-localizing. This test has not been used with SLE subjects, however, SLE patients have been shown decreased cognitive flexibility (Wekking et al., 1991; Denburg et al., 1987). Furthermore, impaired
concept formation and cognitive flexibility have been shown with subcortical syndromes (Huber & Shuttleworth, 1989).

2. Attention/Concentration

TRAIL-MAKING TEST, PART A and B (HRNTB, 1979): a measure of attention and concentration, visual scanning, and psychomotor speed. In part A subjects connect circles with numbers 1-25 as quickly as possible, and in part B, the task is to connect alternating letters and numbers. Time to complete the task is noted. SLE subjects in Wekking et al. (1991) and Denburg et al. (1987) studies showed impairment on this measure.

DIGIT SYMBOL (WAIS-R, Wechsler, 1981): a measure of psychomotor speed, sustained attention, and visual motor coordination. Subjects substitute as many symbols as possible for numbers according to a key in a 90 second interval. Digit symbol consistently been found to be the most sensitive of Wechsler subtests to cerebral damage. Impaired performance on this test was found in Denburg et al. (1987) and Hanley et al. (1992) studies.

PACED AUDITORY SERIAL ADDITION TEST (PASAT; Gronwall & Sampson, 1974): a measure of speed of information processing and sustained attention. Subjects are presented with a random series of digits at four rates of speed, and are required to add each digit to the one preceding it. This test has not been used in any of the neuropsychological studies reviewed. However, individuals with subcortical
syndromes have been found to do poorly on this test (Huber and Shuttleworth 1993).

STROOP COLOR WORD TEST (Golden, 1978): a measure of speed and flexibility of information processing, attention, and concentration. Subjects are presented with three trials: one in which they name as many colors as possible denoted by a name of a different color, one in which they read color words printed in black ink, and one in which they name colors. The number of items read in a 45 second interval is recorded. Wekking et al (1991) found this test to be the only one that differentiated SLE and RA subjects. However, this was not confirmed by the Gingsburg et al. (1992) study.

3. Memory

LOGICAL MEMORY (Immediate and Delayed; Wechsler Memory Scale-Revised, 1987): a measure of immediate and short-term verbal memory and verbal comprehension. Subjects are read two stories and asked to recall each verbatim immediately and after a 30-minute delay. Denburg et al. (1987) found impairment in SLE subjects both with immediate and delayed recall.

REY-OSTERRIETH COMPLEX FIGURE (Spreen & Strauss, 1991): Copy, immediate, and delayed recall: a measure of nonverbal memory visuoperceptual, and visuographic ability. Subjects copy a complex figure, then are asked to reproduce from memory as much of the figure as possible, and again after a 45-minute delay. SLE subjects in the Denburg et al. (1987)
study showed worse performance than controls on delayed recall and copying the figure.

4. Visuospatial

REY-OSTERRIETH COMPLEX FIGURE DRAWING-Copy, as described above.

HOOPER VISUAL ORGANIZATION TEST (Hooper, 1983): a measure of visual gestalt perception. Subjects are presented with pictures of cut-up objects, and their task is to identify the object. This test has not been used with SLE patients, but was selected because it does not involve graphic competency as does the Rey-complex figure, and it is not timed as the Block Design Test.

BLOCK DESIGN (WAIS-R, 1981): a measure of visual-spatial organization, visuomotor, and nonverbal reasoning skills. The test is timed, and requires the subject to duplicate a design presented on a card. This is one of the more sensitive tests on the WAIS-R to cerebral dysfunction, particularly right hemisphere dysfunction. Denburug et al. (1987) and Hanley et al. (1992) studies found SLE subjects to be impaired on this test, however, Wekking (1991) study found no significant differences between SLE subjects and RA controls.

WRITING. The subjects provided a writing sample by writing to dictation 3 items from the Boston Diagnostic Aphasia Examination (Goodglass & Kaplan, 1983). The samples
were evaluated according to the qualitative criteria provided in the test manual.

6. Language

CONTROLLED ORAL WORD ASSOCIATION TEST (COWA; Benton & Hamser, 1989): a measure of verbal fluency. Subjects are asked to generate as many words as possible that begin with a letter c, f or l in 60 seconds. Decreased verbal fluency was found in the studies by Denburg et al. (1987) and Hay et al. (1992).

BOSTON NAMING TEST (BNT; Kaplan et al. 1983): a measure of confrontation naming. The subjects are presented with a series of pictures which they are asked to name. This test has not been used in previous studies, but was selected because language functioning in SLE other than verbal fluency has not been adequately addressed. Confrontation naming is rarely impaired in subcortical dementia syndromes; however, dysarthria and writing problems are common.

Dysarthria was evaluated by using six items (e.g., streptomycin, Massachusetts-Episcopal) from the Luria-Nebraska Neuropsychological Battery (LNNB). The subjects were asked to repeat the words and performance was evaluated according to the qualitative criteria provided in the test manual. If two items were failed, the subject was considered to present with dysarthria.
7. Praxis

Limb and oral apraxia were evaluated with items from the Western Aphasia Battery (Kertesz, 1982). The subjects were asked to perform various gestures and movements such as making a fist, puffing out cheeks, and whistling. Three additional items from the Luria battery were used to assess apraxia of utilization of objects. The subjects were asked to pantomime a motor action or series of motor actions. Performance was evaluated according to the qualitative criteria provided in the test manuals.

SLE patients have shown impairment in previous studies on seven of the tests above (Trail-making A & B, Logical Stories, Rey Complex Figure, COWA, Stroop, Block Design, Digit Symbol), and they were included for cross-validation. Three of the tests have not been used in previous studies (BNT, Category, Hooper, and the PASAT), but were selected because of their possible contribution for detecting patterns of cognitive dysfunction. None of the neuropsychological studies reviewed addressed dyspraxia, dysgraphia, or dysarthria.

Initially, the Grooved Pegboard test, a measure of motor speed and dexterity, was included in the test battery and administered to 29 subjects. However, its use was later abandoned because of possible invalid results. A number of subjects to whom this test was administered achieved very high scores which may have been due to confounding variables.
such as the presence of peripheral neuropathies, Raynaud's syndrome, arthritis, carpal tunnel syndrome, and complaints of pain, swelling, and numbness of fingers. Additionally, subjects with long fingernails could not perform this test efficiently. Inclusion of the Grooved Pegboard test scores in computing the Impairment Score would have resulted in inflated scores that may not reflect CNS dysfunction.

The battery was administered in a standard order for all subjects: Rey-copy and immediate recall, Logical Stories, Stroop, PASAT, Trails A and B, Digit Symbol, Logical Stories-delayed recall, Rey-delayed recall, Category, Hooper, COWA, Block Design, BNT, and the items from the Luria, Boston, and Western aphasia screens.

Data analysis

Statistical analyses were performed with CSS: Statistica, version 5 (StatSoft, 1991). To determine the frequency of cognitive dysfunction, the raw cognitive test scores for each subject were converted to z-scores based on normative data for each test. Premorbid level of functioning for each subject was estimated using the Barona, Reynolds and Chastein (1984) formula and expressed as a z-score. In order to correct for individual differences in premorbid abilities, the obtained z-score for each test was compared to the premorbid IQ estimate and a residual score was calculated. The residual score (adjusted z-score) represents the difference between the subject's predicted and actual
test score. Any test that was greater than 1.5 SD's below the expected level (premorbid IQ) was considered to reflect an area of significant impairment for that individual. The same cut-off was used with unadjusted z-scores.

An Impairment Score was calculated for each subject by summing the unadjusted z-scores. Absolute values for the z-scores were used. A test score at mean or above was given a z-score of 0 indicating no impairment. Writing, dysarthria, and dyspraxia items were evaluated qualitatively, thus not included in the Impairment Score. Frequency counts were used to determine the relative scope and severity of impairment, subjective complaints of cognitive and emotional dysfunction, proportion of subjects impaired on each test, and proportion of subjects who meet the criteria for subcortical dementia.

A standard multiple regression was performed between the Impairment Score as the dependent variable and age, education, depression (BDI) and fatigue (FSS) scores, and duration of steroid use as the predictors. Post hoc analyses were performed using partial correlation coefficients to examine relative contributions of BDI subscale scores to the variance of the Impairment Score. T-tests were used to compare the mean scores on the FSS and the BDI subscales of subjects identified as presenting with subcortical dementia and those who did not meet the criteria. Person correlation
coefficients were computed to examine correlations between memory tests, steroid dosage and duration of steroid use.
CHAPTER 3

RESULTS

Descriptive Data

Table 1 summarizes the demographic features of the 50 subjects. The majority of the subjects were female and Caucasian, only two males participated.

Table 1

Demographic Features of Study Population

<table>
<thead>
<tr>
<th>Measure</th>
<th>Mean</th>
<th>SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>42.3</td>
<td>10.2</td>
</tr>
<tr>
<td>Education (years)</td>
<td>13.8</td>
<td>2.0</td>
</tr>
<tr>
<td>Estimated IQ (z-score)</td>
<td>.5</td>
<td>.4</td>
</tr>
<tr>
<td>Years of symptoms</td>
<td>12.2</td>
<td>9.5</td>
</tr>
<tr>
<td>Years since diagnosis</td>
<td>7.2</td>
<td>5.9</td>
</tr>
<tr>
<td>Female (%)</td>
<td>96</td>
<td></td>
</tr>
<tr>
<td>Caucasian (%)</td>
<td>80</td>
<td></td>
</tr>
<tr>
<td>Employed (%)</td>
<td>42</td>
<td></td>
</tr>
</tbody>
</table>

Three of the subjects had a history of cerebrovascular event related to SLE. A diagnosis of antiphospholipid syndrome was reported by two subjects, and vasculitis by
three. Seven (14%) subjects had had at least one seizure during the course of the illness. One subject reported a history of meningitis, and one a history of psychosis. Headache, experienced at least weekly, was reported by 31 (64%) subjects. A diagnosis of fibromyalgia was reported by 13 subjects (26%). Twenty-five subjects (50%) were taking oral corticosteroids, at a mean dosage of 7.32 mg/day (range 1-18 mg/day). The majority of subjects (88%) were taking second-line medications, most commonly Plaquenil (40%). Nineteen subjects (38%) were regularly taking antidepressant/anxiolytic medications.

The frequencies of self-reported symptoms of cognitive difficulties currently experienced as assessed by Neuropsychological Symptom Checklist are reported in Table 2. Symptoms endorsed by more than 25% of the subjects are displayed.

The endorsed problems with writing were often reported to be related to decreased ability to spell or difficulties with writing composition rather than writing mechanics. Problems with speech were attributed to slurring of words or word-finding difficulties. Some subjects reported having experienced severe transient cognitive symptoms such as being unable to read at all or short-periods of acute confusion and disorientation to time, place, and situation. Several subjects reported increased cognitive dysfunction
<table>
<thead>
<tr>
<th>Symptom</th>
<th>Percent</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Have memory problems</td>
<td>66</td>
</tr>
<tr>
<td>2. Can't think as quickly as before</td>
<td>64</td>
</tr>
<tr>
<td>3. Remembering the right word when talking</td>
<td>58</td>
</tr>
<tr>
<td>4. More easily distracted</td>
<td>56</td>
</tr>
<tr>
<td>5. Find it hard to think clearly</td>
<td>48</td>
</tr>
<tr>
<td>6. Can't concentrate</td>
<td>46</td>
</tr>
<tr>
<td>7. Following conversation</td>
<td>34</td>
</tr>
<tr>
<td>8. Understanding others</td>
<td>28</td>
</tr>
<tr>
<td>9. Problems with speech</td>
<td>28</td>
</tr>
<tr>
<td>10. Problems with writing</td>
<td>26</td>
</tr>
</tbody>
</table>

when experiencing a flare, on high doses of steroids or when fatigued. Emotional problems commonly reported by the subjects included depression (54%), tension and anxiety (56%), anger (42%) and loss of interest (34%).

Nine of the 21 subjects employed outside of home reported change in their work performance in the previous six months. Two reported improved performance, others reported worse performance attributed to increased fatigue, disorganization, memory and word-finding problems, and decreased task completion time. Fifteen of the 29 subjects
not employed outside of home were either on permanent disability or unable to work due to SLE. Fourteen were homemakers, students or looking for a job.

**Prevalence and Severity**

Table 3 shows the number and percentage of protocols rated as none/mild (0-2 tests performed in the impaired range), moderate (3-4 tests impaired) and severe (more than 5 tests impaired) cognitive dysfunction using the adjusted and unadjusted z-scores.

**Table 3**

**Severity Ratings of Test Protocols**

<table>
<thead>
<tr>
<th>Score</th>
<th>None/Mild</th>
<th>Moderate</th>
<th>Severe</th>
</tr>
</thead>
<tbody>
<tr>
<td>adjusted-z</td>
<td>12 (24%)</td>
<td>10 (20%)</td>
<td>28 (56%)</td>
</tr>
<tr>
<td>z</td>
<td>30 (60%)</td>
<td>13 (26%)</td>
<td>7 (14%)</td>
</tr>
</tbody>
</table>

Using a criterion of 3 or more tests performed in the impaired range with adjusted z-scores, a total of 38/50 (76%) of SLE subjects were determined to be cognitively impaired. For unadjusted z-scores the prevalence rate was 20/50 (40%). Although a substantial proportion of subjects achieved a rating of severe and presented with wide-ranging cognitive dysfunction, only 8/50 (16%) met the Cummings and Benson (1983) criteria for dementia, i.e., impairment of 2 SD's or greater below normative mean of at least three out
of five areas of function: memory, visuospatial, mood, cognition, and language. Scores of 2 SD's or greater below the mean were rare when test performance was evaluated using normative data alone, but occurred with some frequency when performance was compared to estimated premorbid IQ. Most subjects who were identified as cognitively impaired presented with at least one score of 2 SD's below the expected level of performance. In the severe group, fifteen of the subjects presented with 7 or more impaired test scores. Overall, cognitive dysfunction in SLE appears diffuse, with several areas of cognition impaired, but less severe than observed with some other neurologically impaired populations i.e., Alzheimers.

Pattern of Dysfunction

Table 4 shows the means, standard deviations and probability values derived from t test comparisons between the obtained means and the normative means for each test for which means and standard deviations were available, if unavailable, T scores are presented. The proportion of subjects impaired on a given tests is also shown using the adjusted (Az) and unadjusted z scores.

The most common cognitive deficits presented by the SLE patients in the sample were conceptual reasoning/abstract thinking, cognitive flexibility, sustained attention, speed of information processing, visual memory and verbal fluency. Confrontation naming, visual perception, and recall of
Table 4

Neuropsychological Test Measures and Proportion Impaired

<table>
<thead>
<tr>
<th>Test Measure</th>
<th>M</th>
<th>SD</th>
<th>p</th>
<th>z</th>
<th>Az</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abstract/Conceptual Reasoning</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Booklet Category total errors</td>
<td>66.72</td>
<td>31.72</td>
<td>&lt;.001</td>
<td>30%</td>
<td>58%</td>
</tr>
<tr>
<td>Psychomotor speed/Attention</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Trails A total time</td>
<td>33.38</td>
<td>12.24</td>
<td>0.03</td>
<td>14%</td>
<td>38%</td>
</tr>
<tr>
<td>Digit Symbol age-corrected score</td>
<td>10.62</td>
<td>2.25</td>
<td>NS</td>
<td>0%</td>
<td>36%</td>
</tr>
<tr>
<td>Speed of Information Processing/Cognitive Flexibility/Attention</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stroop Interference Word # of items</td>
<td>95.18</td>
<td>11.35</td>
<td>T = 43</td>
<td>4%</td>
<td>40%</td>
</tr>
<tr>
<td></td>
<td>Color # of items</td>
<td>68.20</td>
<td>10.14</td>
<td>T = 42</td>
<td>16%</td>
</tr>
<tr>
<td></td>
<td>Color/word # of items</td>
<td>41.40</td>
<td>17.66</td>
<td>T = 46</td>
<td>30%</td>
</tr>
<tr>
<td>PASAT</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Trial 1-#correct</td>
<td>33.38</td>
<td>12.24</td>
<td>&lt;.001</td>
<td>28%</td>
<td>52%</td>
</tr>
<tr>
<td>Trial 4-#correct</td>
<td>21.54</td>
<td>10.17</td>
<td>0.002</td>
<td>38%</td>
<td>56%</td>
</tr>
<tr>
<td>Trails B total time</td>
<td>70.90</td>
<td>31.12</td>
<td>NS</td>
<td>8%</td>
<td>22%</td>
</tr>
</tbody>
</table>

(Table continues)
<table>
<thead>
<tr>
<th>Test Measure</th>
<th>M</th>
<th>SD</th>
<th>p</th>
<th>z</th>
<th>Az</th>
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</thead>
<tbody>
<tr>
<td><strong>Memory</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Immediate-verbal Logical Memory</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>total recall</td>
<td>23.92</td>
<td>7.68</td>
<td>NS</td>
<td>12%</td>
<td>34%</td>
</tr>
<tr>
<td>Immediate-visual Rey Complex Figure</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>total recall</td>
<td>15.74</td>
<td>7.40</td>
<td>0.03</td>
<td>36%</td>
<td>66%</td>
</tr>
<tr>
<td>Recent-verbal Logical Memory</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>total recall</td>
<td>21.18</td>
<td>8.02</td>
<td>NS</td>
<td>8%</td>
<td>28%</td>
</tr>
<tr>
<td>Recent-visual Rey Complex Figure</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>total recall</td>
<td>15.36</td>
<td>7.31</td>
<td>0.02</td>
<td>44%</td>
<td>70%</td>
</tr>
<tr>
<td><strong>Visuospatial</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hooper Visual Organization Test</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>T-score</td>
<td>51.72</td>
<td>5.56</td>
<td>T = 52</td>
<td>2%</td>
<td>26%</td>
</tr>
<tr>
<td>Block Design age-corrected scores</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rey Complex-copy total score</td>
<td>10.26</td>
<td>2.79</td>
<td>0.05</td>
<td>10%</td>
<td>30%</td>
</tr>
<tr>
<td><strong>Language</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Boston Naming Test total score</td>
<td>56.78</td>
<td>3.67</td>
<td>NS</td>
<td>4%</td>
<td>16%</td>
</tr>
<tr>
<td>Controlled Oral Word Association Test</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>total score</td>
<td>36.14</td>
<td>10.25</td>
<td>T = 47</td>
<td>14%</td>
<td>42%</td>
</tr>
</tbody>
</table>

**NS** Not significant (p > .0.05)
paragraph length material were relatively unimpaired for most subjects. Group comparisons with normative groups of each individual test yielded significant differences with PASAT, Rey Complex Figure, Block Design, Trails A and Booklet Category.

The proportion impaired for each test was significantly higher when adjusted z-scores were used, as would be expected. However, the same deficits emerged using normative data alone.

Dysarthria, dyspraxia and dysgraphia were evaluated qualitatively and not included in any of the data analyses. None of the subjects presented with dysarthria, although mild slurring of words was observed with four subjects.

The performance of all subjects on limb and oral apraxia items from the Western Aphasia Battery was within normal limits. All subjects were able to pantomime motor sequences without difficulty. Eight (16%) subjects used a body-part-as-object which is uncommon in neurologically intact subjects. Dysgraphia was presented by two subjects. Overall, the subjects had good writing skills with no impairment in writing mechanics noted.

To evaluate the hypothesis that patients with SLE present with a pattern of cognitive dysfunction that resembles the pattern seen in subcortical dementias i.e., slowed information processing speed, impaired concept formation, decreased attention and concentration, memory
deficits, mood disturbance, and absence of aphasia, apraxia and agnosia, the proportion of individuals meeting these criteria was calculated. The PASAT, Stroop, Booklet Category, and Logical Memory and Rey Complex Figure delay scores were used to determine the presence of a subcortical dementia pattern. A subject was identified to present with this pattern if impaired adjusted z-scores were observed in 3/5 tests including Stroop and/or PASAT. As previously discussed, none of the subjects showed evidence of aphasia, apraxia or agnosia. This criterion was not used to determine the presence of subcortical dementia as it may have led to over-identification of subjects with this pattern.

Twenty-eight (56%) subjects showed evidence of subcortical-type dementia based on the cognitive variables alone. This represents 74% of those identified as cognitively impaired (3 or more impaired scores). Mood disturbance, defined as a total BDI score of 16 or greater, was reported by twelve (43%) subjects presenting with the subcortical pattern, and by 5 (23%) subjects who did not meet the criteria.

Role of Medications, Depression and Fatigue

A standard multiple regression was performed with the Impairment Score as the dependent variable and age, education, total BDI scores, total FSS scores, and duration of steroid use as the predictors. The variables were entered in the equation in the above order.
Initially, cumulative steroid dosage for the previous six months was to be used as one of the independent variables. However, the distribution of this variable was highly positively skewed and various transformation did not significantly improve linearity. The distribution was skewed because a half of the subjects had not been on corticosteroids in the previous six months and the average dosage was very low at 7.32 mg/day (1-18 mg/day). It is unlikely that such low dosages would have a significant effect on cognitive functioning. Duration of steroid use was selected because of the reports of long-term use possibly producing cortical atrophy and decline in cognitive functioning. Duration of steroid use was highly correlated with the duration of illness (time since diagnosis), thus duration of illness was not included in the analysis to avoid redundancy. Other medication use was also considered as one of the predictors. However, the majority of subjects (88%) were taking prescribed medications, many subjects taking a variety of different types, thus any association between cognitive dysfunction and medication use would have been difficult to ascertain. Age and education are commonly associated with cognitive test performance and thus included in the predictors. Bonferroni's adjustment for multiple comparisons was applied. With five predictor variables the level of significance was $p < .01$. 
An evaluation of assumption revealed no significant violations. Most variables were slightly positively skewed, but only steroid duration was significantly skewed. Transformations with this variable were attempted, but did not improve normality. One univariate outlier (long duration of steroid use) among the cases was found, and was retained. There were no missing variables.

Table 5 displays the correlations between variables, the unstandardized regression coefficients (B), the standardized regression coefficients (beta), and the intercept. R for regression was significant, F(5,44) = 5.69, p < .001. Two of the IV's contributed significantly to prediction of the level of cognitive impairment; education (sr = .10) and total BDI scores (sr = .07). All the IVs in combination contributed another .22 in shared variability. Altogether, 39% (32% adjusted) of the variability in cognitive impairment was predicted by the independent variables.

Fatigue was significantly correlated with the Impairment Score (p = .01), but appears redundant to the relationship between the Impairment Score and other IVs in the set. Changing the order of entry of variables with the FSS entered first did not produce different results. Age was expected to be associated with cognitive impairment, but did not account for a significant proportion of the variance in
cognitive impairment. Most subjects were relatively young (mean age = 42.2 years, SD = 10.21).

Table 5
Results of Multiple Regression

<table>
<thead>
<tr>
<th>Impairment</th>
<th>Variables (DV)</th>
<th>Age</th>
<th>Educ</th>
<th>BDI</th>
<th>FSS</th>
<th>B</th>
<th>Beta</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>.16</td>
<td>.07</td>
<td>.10</td>
<td>.07</td>
<td>.18</td>
<td>.43**</td>
<td></td>
</tr>
<tr>
<td>Educ</td>
<td>-.47</td>
<td>-.11</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BDI</td>
<td>.52</td>
<td>.07</td>
<td>-.31</td>
<td></td>
<td></td>
<td>.31</td>
<td>.36*</td>
</tr>
<tr>
<td>FSS</td>
<td>.35</td>
<td>.07</td>
<td>-.13</td>
<td>.62</td>
<td></td>
<td>.41</td>
<td>.09</td>
</tr>
<tr>
<td>Steroid</td>
<td>.04</td>
<td>.07</td>
<td>.02</td>
<td>-.04</td>
<td>.08</td>
<td>.01</td>
<td>.08</td>
</tr>
</tbody>
</table>

$R^2 = .39$  Intercept = 18.46
adjusted $R^2 = .32$

$R = .63$***

* p < .05, ** p < .01, *** p < .001

The relationship between depression and cognitive impairment was further investigated by examining scores on the two subscales of the BDI: Cognitive-Affective and Somatic-Performance. Their relative contributions as predictors of cognitive impairment was assessed by partial correlation. It was suspected that the SLE subjects may be
endorsing somatic symptoms which are common in SLE i.e., fatigue, sleep disturbance, that elevate the depression scores. The total BDI scores did not significantly predict the level of cognitive impairment when somatic symptoms were partialled out ($r = .09, p = .6$) The somatic symptoms subscale scores were significantly correlated with the Impairment Index scores ($r = .31, p = .03$).

Mood disturbance is commonly associated with the subcortical dementia pattern. As previously stated, more subjects with subcortical-type dementia (43%) presented with total BDI scores 16 or greater as compared to subjects without an identified pattern or no cognitive impairment (23%). Independent t-tests were used to examine the mean differences between the two groups on the Somatic-Performance and Cognitive-Affective subscales of the BDI and the Fatigue Severity Scale. The mean scores on the Cognitive-Affective subscale and the Fatigue Severity Scale were not significantly different between the two groups, but significant differences were found between the Somatic-Performance subscale mean scores ($t(48), p = .004$).

To investigate the possibility that the subcortical dementia pattern was associated with greater disability and perhaps greater disease activity, the proportion of individuals currently employed outside of home in both groups was compared. More individuals in the subcortical dementia group were employed 13/27 (48%) than in the
comparison group 10/24 (42%), but the difference was not significant ($p = .41$). It does not appear that the subjects in the subcortical group were more disabled, fatigued or depressed, although they reported more vegetative symptoms of depression.

Correlational analyses were performed between cumulative steroid dosage, duration of steroid use and immediate and delayed memory scores on the Rey Complex Figure and the Logical Memory because of recent reports of corticosteroids adversely affecting memory. None of the correlations were significant.
CHAPTER 4

DISCUSSION

The results of the study yielded an overall prevalence of cognitive impairment of 76%. The prevalence rate without correcting for individual differences in premorbid cognitive ability was 40%. These prevalence rates are similar to the rates reported in other studies that used comprehensive neuropsychological batteries to assess cognitive impairment (Wekking et al., 55%; Carbotte et al., 1986; 66% overall, 87% for the NPSLE group). It should be noted, that in the present study, a more liberal cutoff for cognitive impairment (greater than 1.5 SD below mean) was used. Most of the previous studies used a cutoff of 2 SD or greater below the mean. If the 2 SD cutoff is used, the rate of prevalence is 62%. Many studies appear to have grossly underestimated the prevalence of cognitive dysfunction in SLE, possibly due to using very limited test batteries and insensitive measures of cognitive dysfunction, overly conservative criteria for identifying deficits, and inappropriate control groups.

The obtained prevalence rate was higher than expected given that the sample was recruited from the community. Clinic-attending samples were used in most previous studies.
The prevalence rate may be an overestimate, because the sample was self-selected and may have contained a disproportionate number of individuals with concerns about their cognitive functioning. On the other hand, subjects with a severe illness or physical disability were not included. All of the subjects were ambulatory, independent in ADL's, and 42% were employed. The majority of the subjects appeared to present with relatively mild disease activity at the time of testing or were in remission. Twenty-six percent reported current or past CNS involvement which is less than the reported proportion in many other studies. However, the true proportion of those with documented CNS involvement may be higher in this sample. The study relied on self-report, medical records were not reviewed for neuropsychiatric symptoms, clinical examinations or diagnostic studies were not performed. The obtained prevalence rate suggests compromised CNS functioning in the majority of subjects.

Three patients with a history of CVA's related to SLE were included in the sample. Their exclusion from the analyses was considered, but all of the three subjects showed a diffuse pattern without any definite lateralizing signs. One of these subjects had a diagnosis of antiphospholipid syndrome, and she was included in the subcortical dementia group. Another subject had a diagnosis of vasculitis, but showed only mild diffuse dysfunction. The
third subject reported multiple small infarcts and TIA's. Her neuropsychological test scores indicated moderate to severe impairment in most areas of function. She was included in the group identified as presenting with dementia.

The majority of the SLE patients in this sample presented with wideranging cognitive dysfunction, and a substantial percentage (56%) showed impairment in more than 5 neuropsychological tests. The severity of dysfunction, however, appears relatively mild, with only 16% meeting the criteria for dementia used in the study. It is debatable whether many of the subjects identified as cognitive impaired, would meet the DSM-IV criteria for dementia. Severe memory dysfunction does not appear to characterize this sample and no subjects presented with apraxia, aphasia or agnosia. Furthermore, approximately a half of those identified as cognitively impaired were employed, thus seemed to be able to compensate for their deficits. It is postulated, however, that all of the subjects identified as cognitively impaired would meet the diagnostic criteria for a mild neurocognitive disorder, a research diagnosis in the DAM-IV.

The prevalence rates are higher when the test scores are compared to an estimated premorbid level rather than based on normative data alone. The mean IQ (107.2) for this sample was somewhat higher than in the general population.
The premorbid estimate was used because it was felt that some type of individual comparison standard was necessary in order to identify areas of dysfunction and possible patterns. There is ongoing debate in the neuropsychological literature as to what is the best method of evaluating premorbid ability. The Barona, Reynolds and Chastain (1984) formula may not be among the best as it tends to underestimate high IQ's and overestimate low IQ's. If that is the case with the subjects in the study, then the deficits may be even greater in severity. Nevertheless, the obtained results support the first hypothesis regardless of whether normative data is used alone or the test results are evaluated based on the expected level of performance. Ideally the study would have employed an age and education matched control group with a chronic illness that does not involve the central nervous system to aid in determining at what cutoffs should be used for cognitive impairment. However, comparing group mean scores may not have provided much useful information, and this method is particularly problematic in a heterogeneous population such as SLE were standard deviations are typically high and a substantial proportion of subjects are unimpaired. The group comparison method may have prevented findings of significant differences in previous studies and account for some of the inconsistencies in the literature with regard to prevalence rates and specific deficits.
The pattern of neuropsychological impairment of SLE patients resembles the pattern observed in frontal lobe dysfunction and in subcortical dementias with diffuse white matter involvement such as MS and HIV. It should be noted, that the term subcortical dementia in this study does not refer to specific location of neuropathological alteration, but is used to describe a pattern of cognitive impairment.

The most common deficits observed were visual memory, abstract/conceptual reasoning, verbal fluency, speed of information processing, attention and concentration, and cognitive flexibility. Impairments were less frequent seen with confrontation naming, visual perception, psychomotor speed, and verbal memory. Apraxias, aphasias or agnosias were not observed.

The neurocognitive test performance of the subjects is similar to that found in previous studies, with the exception of verbal memory and psychomotor speed. Other studies using the same tests found significant differences when age, education, and sex matched control groups were used. Impaired scores on the Logical Memory with immediate and delayed recall, on Trails A and B, and Digit Symbol were found by Carbotte et al. (1986). Digit symbol scores were found to be impaired by Hanley et al. (1992). Impaired performance on Trails A and B were observed by Wekking et al. (1991). The differences in findings between the present and previous studies may have been due to using normative
data instead of a matched control group to evaluate cognitive test performance. This sample consisted primarily of women. Female superiority on symbol substitution tasks have been documented by several studies (Lezac, 1995).

The most frequently impaired tests were the Rey Complex Figure, immediate and delayed recall, and the Booklet Category. The Rey Complex Figure mean scores were similar to those obtained in the Carbotte et al. (1986) study, but the proportion impaired in the present study was higher. On this test, the subjects are not told that they have to reproduce the figure later from memory, which may partially account for the very deficient recall of many subjects as compared to their performance on the Logical Memory. Furthermore, many subjects copied the figure in a piecemeal fashion i.e., coping it from left to right or starting with small details rather than conceptualizing the figure as a whole and filling in the details later. This type of an approach shows poor planning and is associated with frontal lobe dysfunction. Studies have shown that this approach often leads to impaired recall of the figure (Spreen & Strauss, 1991). Most subjects were able to copy the figure accurately regardless of the approach used, indicating intact visuographic skills.

Impaired verbal memory was uncommon in this sample. The group mean score was not significantly different from the normative mean. The present study does not shed much light
on verbal memory in SLE i.e., whether memory impairment is due to impaired encoding, storage or retrieval. Inclusion of learning measures such as the California Verbal Learning Test (CVLT) or the Bushke Selective Reminding Test could have better delineated the nature of verbal memory deficits in SLE, and perhaps provided support for the subcortical dementia hypothesis as well. The CVLT was used in one previous study which reported difficulties primarily with retrieval (Hanley et al., 1992).

Deficits in abstract reasoning and concept formation were very common and relatively severe for the group as a whole and for individual patients. Many well-educated subjects performed in the moderate to severe impairment range using the Halstead-Reitan classification of impairment for this test. The Booklet Category was not used in any of the previous studies reviewed. However, its use should be considered in future studies and in clinical practice as it appears to be very sensitive to cognitive dysfunction in SLE.

The overall pattern and the type of deficits presented by individual subjects provide support for the subcortical dementia hypothesis. There is no evidence from diagnostic studies that frontal lobes are preferentially involved in SLE. The most common findings for NPSLE patients without focal manifestations are multiple lesions predominately in the subcortical and deep white matter and hyperintensity
bordering the lateral ventricles. Cognitive dysfunction for some SLE patients may result from disconnections between subcortical and cortical structures due to white matter changes and present as frontal lobe dysfunction because of the extensive connections between subcortical structures and the frontal lobes. One recent study concluded that patients with diffuse periventricular and white matter lesions show a neuropsychological profile that resembles subcortical dementia (Libon, Bogdanoff, Bonvita, Cloud, Tesh, Cash, & Ball, 1997). Motor dysfunction is common in subcortical syndromes, but subjects in this sample did not appear to present with significant motor impairment based on their performance on the psychomotor measures. However, fifty-six percent of subjects reported problems with balance and/or coordination.

The subjects in the subcortical dementia group achieved higher total BDI scores due to endorsing more somatic symptoms of depression. They did not differ from those without an identifiable pattern or no cognitive impairment on ratings of fatigue or cognitive-affective symptoms of depression. They did not appear to be more physically disabled. These subjects frequency endorsed symptoms such as negative perceptions of self, loss of energy and motivation, decreased appetite, weight loss, loss of interest in sex and concerns about health. These findings are consistent with the subcortical dementia hypothesis. Mood disturbance in
subcortical dementia syndromes is often described as apathy, loss of interest and motivation. In subcortical dementias, fundamental functions such as arousal, attention and concentration, processing speed, motivation, and mood are affected. In contrast, instrumental functions such as language skills, perception and praxis are affected in cortical dementias. The subjects in the subcortical dementia group appear to present with impaired fundamental functions, with instrumental functions relatively intact.

Alternative hypothesis for subcortical dementia is that a diffuse brain dysfunction, structural and/or biochemical produces the pattern observed. Goldberg (1986) suggested that diffuse CNS disruption masquerades as frontal-subcortical dysfunction. This remains a viable alternative hypothesis for the pattern observed in this study. SLE subjects present with diffuse cognitive deficits. Widespread lesions are reported in diagnostic studies, although in some cases of NPSLE, no structural abnormalities are found. SLE patients often have multiple organ involvement. In this sample, subjects reported of thyroid, kidney, liver, lung, and cardiovascular involvement. In addition, they were taking various medications which may affect CNS function. Given the myriad of factors that could cause CNS dysfunction in SLE, it is somewhat surprising that consistent deficits and an identifiable pattern was found.
It is speculated that many of the subjects in this study who were identified as cognitively impaired would not show any structural changes in diagnostic studies. In fact, some subjects reported of undergoing MRI scanning because of suspected CNS involvement, and nothing of significance was found. Previous studies have shown that individuals with subclinical CNS involvement may not show any abnormalities with MRI or CT, but show abnormalities with PET (Carbotte, 1992). In some cases, the cognitive dysfunction may be due to biochemical and immunological changes that are transient or reversible. However, many of the subjects in this study complained of long-standing cognitive dysfunction that may fluctuate in severity, but does not resolve.

The results of the multiple regression analysis indicate that cognitive dysfunction in SLE is associated with somatic symptoms of depression and education. Fatigue is correlated with cognitive impairment and self-reported depression, but it is not a significant predictor of the level of impairment when depression and educational achievement are taken into account. The finding that depressive symptoms, particularly somatic symptoms, are associated with cognitive impairment is significant. Previous studies generally concluded that there was no relationship between cognitive symptoms and depression. The BDI was not used in any of the studies reviewed, and no other study attempted to separate somatic and affective
symptoms. If the results of the present study are replicable with other SLE samples, the findings of previous studies in which self-report measures of depression were used become questionable.

It is speculated that the somatic symptoms of depression may be related to CNS dysfunction. The finding that depressive symptoms correlate with documented CNS involvement and are not associated with any other disease manifestations or organ involvement (Utset et al., 1994) provides some support for this hypothesis.

An alternative explanation is that the cognitively impaired subjects had a more active and/or severe disease, thus endorsed more somatic symptoms. This cannot be ruled out as no disease activity measures were used. However, most studies have not found an association between cognitive impairment, disease activity, or specific organ involvement. Furthermore, those identified as cognitively impaired were as likely to be employed as those who were not.

The study did not find support for the recent reports of a low dose, short-term use of corticosteroids producing verbal memory impairment (Keenan, 1996). Steroid dosage or duration of use were not associated with verbal or visual memory impairment or overall cognitive functioning in this sample.

Subjects' self-reported cognitive difficulties corresponded fairly closely with the objective findings. The
subjects complained of memory problems, difficulties with concentration, thinking clearly and quickly, following conversation, understanding others, and word-finding problems. The subjects seemed to be very aware of their cognitive difficulties, and their subjective assessment of their cognitive functioning was often corroborated by objective findings. However, subjective complaints of memory dysfunction did not always correlate with measurable impairment. The reported memory difficulties may be related to slowed speed of processing and decreased attention and concentration.

In summary, the findings of this study indicate: (1) cognitive dysfunction in SLE is very common and has been underestimated by many of the previous studies; (2) the pattern of dysfunction resembles that observed in subcortical dementias; (3) most cognitively impaired SLE patients present with mild, diffuse dysfunction; (4) cognitive dysfunction is associated with somatic symptoms of depression; (5) fatigue is not a significant predictor of the level of cognitive impairment; (6) duration of steroid use is not correlated with overall cognitive impairment or memory impairment; (7) Subjective reports of cognitive dysfunction appear to correlate with objective findings.

The implications of these findings are that SLE patients may need to be routinely questioned with regard to cognitive symptoms by their physicians, and followed-up by
further evaluations including neuropsychological, neurological exams, and brain scan studies when significant changes in cognitive functioning are reported.

Neuropsychological evaluations or screens may be justified for all SLE patients presenting with subjective cognitive complaints to provide baseline information and for early detection of subclinical CNS activity. Neuropsychological evaluations may also be appropriate for patients presenting primarily with vegetative symptoms of depression.

Neuropsychological batteries used to evaluate SLE patients should be comprehensive, given that typically many functions are affected, and the emphasis should on the measurement of speed of processing, attention and concentration, reasoning, learning and memory. Traditional instruments such as the Halstead-Reitan, the WAIS-R, and the Mini-Mental State Exam appear to be insensitive to the types of deficits SLE patients present. Cognitive remediation may be beneficial for patients with persistent, residual cognitive deficits. Several subjects reported using compensatory strategies such as memory notebooks or writing lists. Some patients may benefit from the initiation of steroid treatment when presenting with a decline in cognitive functioning even in the absence of overt clinical evidence of acute CNS involvement.

When evaluating depression in SLE by using self-report measures, clinicians should perform an item, subscale, or
supplementary scale analysis prior to making recommendations about treatment. On the MMPI-2, high elevations on some of the scales can be achieved by endorsing physical symptoms alone. Psychotherapy may not be very effective for a SLE patient who is presenting primarily with somatic symptoms of depression, but treatment with anti-depressants, particularly those with a stimulatory effect in the CNS, may be beneficial. Overall, the cognitive dysfunction in SLE could be characterized as general mental inefficiency, and the mood disorder as under-arousal. The findings suggest that cognitive and depressive symptoms are associated, but the relationship may not be causal. They may be independent manifestations of compromised CNS functioning.

In future research in mood disorders in SLE, including anxiety, the relative contributions of somatic and affective symptoms should be examined prior to drawing conclusions about possible associations with other factors. Given the heterogeneity of SLE, and the apparently fluctuating nature of cognitive impairment, cross-sectional, group designs may be of little value in discovering something of a biological significance related to cognitive dysfunction. Longitudinal single-subject designs with repeated neuropsychological, immunological, and neurodiagnostic studies may be more illuminating as to the possible pathogenic mechanisms that account for the deficits observed.
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group deficits. *Journal of Clinical and Experimental Neuropsychology*, 9, 323-339


