Published in final edited form as:

Neuropsychol Rev. 2008 June ; 18(2): 149–166. doi:10.1007/s11065-008-9061-2.

Neuropsychological Impairment in Systemic Lupus Erythematosus: A Comparison with Multiple Sclerosis

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Abstract

In this manuscript, we review literature describing the neuropsychological and brain imaging characteristics of systemic lupus erythematosus (SLE) patients. The findings are compared and contrasted with multiple sclerosis (MS) studies, revealing similarities and differences of interest to clinicians and researchers. While cognitive impairment is somewhat less common in SLE than MS, the diseases share a similar cognitive profile with deficits most prominent on tests emphasizing the speed of information processing, working memory, and visual/spatial learning, and memory. In early or more mildly affected patients, diffuse white matter damage, which may not be apparent on conventional brain imaging, plays a major role in clinical presentation and cognitive testing. The causes of white matter damage are very different, however, and in later stages of the disease MS and SLE appear to give rise to different forms of cerebral pathology. MS may be characterized by increasing brain atrophy affecting especially the cortical and deep gray matter, at least after conversion to secondary progressive course. There is less evidence for neurodegenerative changes in SLE, but patients are increasingly at risk for cerebrovascular disease. We conclude by offering some suggestions for future clinical and imaging research.

Keywords

Systemic lupus erythematosus; Multiple sclerosis; Cognition; Memory; Processing speed; MRI; Effect size

Systemic lupus erythematosus (SLE) is a relapsing-remitting autoimmune disease with wide ranging organ involvement and clinical symptoms varying from mild and transient symptoms to death. Cognitive impairment is reported in SLE, even among those patients without documented or overt signs of central nervous system (CNS) involvement. Presumably, cognitive disorder is the result of underlying brain disease although the precise mechanisms remain to be elucidated. The prevalence and degree of cognitive impairment is also uncertain.

In this article we will endeavor to evaluate the evidence for neuropsychological impairment in SLE, and to compare the findings with that of MS, another immunological disorder whose symptoms wax and wane and which affects women more than men. Unlike SLE, MS is a disease that always impacts the CNS, and the causes of cognitive disorder in MS are better understood.

Further, there is also consensus regarding the frequency and type of cognitive impairment in MS, and the impact of on quality of life (Benedict et al. 2006a, 2002b; Rao et al. 1991a). In this review, we appraise the evidence for cognitive impairment in SLE and seek to better understand its quality and severity, as well as its brain MRI correlates.

Cerebral Pathology in SLE

In autoimmune disease, immune cells act on the self tissues as if they were foreign, thereby causing injury to multiple organ systems (Kyttaris and Tsokos 2003; Tsokos and Liossis 1998; Vyse and Kotzin 1998). In some ways, SLE is a model autoimmune disease in that both cellular and humoral reactivity to multiple soft-tissues can potentially injure every organ in the body (Vasileios et al. 2006).

The mental status of SLE patients can be temporarily affected by multiple, transient metabolic and systemic processes (Joseph et al. 2007; Scolding and Joseph 2002). For example, pleocytosis can develop within the CSF leading to low grade encephalopathy or subacute confusional state (Scolding and Joseph 2002). Meningeal inflammation may occur in up to 20% of SLE patients (Ellis and Verity 1979). Increased intracranial pressure can arise from a hypercoagulability state or thrombosis within the cerebral venous system (Vidailhet et al. 1990; West 1994). Psychosis is well known in SLE and can indirectly influence cognitive performance (Wekking 1993; Wekking et al. 1991). While these and other transient or fluctuating processes are clinically important, it is the underlying cerebral disease which is of most relevance for the neuropsychology researcher.

More permanent cerebral damage has been attributed to neural injury that may be brought about by pathology involving the cerebrovascular system. Early histopathological work revealed evidence of small vessel vasculopathy in the SLE brain (Ellis and Verity 1979; Johnson and Richardson 1968). This early research showed destructive and proliferative changes involving small vessel walls with extravasations of fibrin and red blood cells, probably leading to thrombosis and more rarely hemorrhage. Another likely mechanism of neuronal injury is brought about by abnormalities in the generation and regulation of autoantibodies which target neuronal tissue. Thus, neuropathology in SLE may arise from either (a) small vessel disease leading to ischemic or hemorrhagic injury and/or (b) autoantibody-mediated injury to target neural cells. Large vessels may also be affected leading to transient ischemic attacks or irreversible stroke in a minority of cases (Scolding and Joseph 2002).

The neurological and psychiatric manifestations of SLE reflect either transient or chronic injury to the CNS, and one may assume that similar processes contribute to neuropsychological testing abnormality in this disease. The reported percentage of patients with neuropsychiatric involvement has varied in the literature due to a lack of uniform clinical criteria (Glanz et al. 1997b). In 1999, an American College of Rheumatology (ACR) ad hoc committee (American College of Rheumatology 1999) defined 19 neuropsychiatric (NP) SLE features or syndromes, categorized as either central or peripheral nervous system, and focal or diffuse (Table 1). The committee designated the term “NP-SLE” as favorable over “CNS-SLE” because of its more comprehensive inclusion of both central and peripheral nervous system disorders. Throughout the literature, however, patients with SLE with one or more of these features are often categorized as having CNS- or NP-SLE, or as having no prior history of CNS (or NP) involvement.

It is important to note that cognitive impairment is included as one of the neuropsychiatric syndromes for classification as NP-SLE which creates a tautological problem when studies are designed to determine the frequency of cognitive impairment in CNS- or NP-SLE. One might ask whether or not the standards in Table 1 are valid for patients who have not undergone neuropsychological assessment. Moreover, NP involvement encompasses a wide range of

disturbances from overt, focal syndromes most often resulting from completed stroke, to acute paroxysmal syndromes such as TIA, seizures, and psychosis, and finally to more diffuse and questionable NP disturbances such as mood disorder and headache. In the ACR report it was recognized that classification of psychiatric disorders and cognitive deficits is difficult and further study is needed.

More recently, patients with SLE with overt disturbances in the more severe range of neurologic or psychiatric involvement tend to be classified as either NP-SLE. Many SLE patients present with no or only subtle cognitive disturbances and these patients are usually classified as “Non-CNS SLE.” While consensus regarding these diagnostic considerations is improving (Kozora et al. 2004, 2007), the classification scheme nevertheless presents a major problem for this review, and perhaps the literature in general. From our perspective, the patient with SLE of most interest to the behavioral neuroscientist is one whose brain is affected, but without the influence of focal or large cerebral lesions, or acute illness such as meningitis. In other words, we are seeking to understand the impact of subtle, generalized cerebral disease without the confounding effects of, for example, large vessel stroke. Within this subset of patients with SLE, the central neuropsychological issue is if cognitive capacity is affected by the subclinical cerebrovascular and autoimmune processes discussed above. Therefore, our review of the literature is not restricted to either NP- or non-CNS SLE. Rather, when possible, we are going to focus our attention on SLE studies in which patients with focal brain injury, such as stroke, were either excluded or the effects of such pathology were accounted for in design or data analysis.

Brain Imaging Findings in SLE

MRI is the current gold standard in the imaging assessment of patients with SLE both for brain and spinal pathologies. The most common conventional brain MRI findings include multiple hyperintense foci in the deep white matter, large territorial infarcts, and more rarely diffuse atrophy and focal hemorrhage. These abnormalities are similar to those seen in many demyelinating, inflammatory, or vascular diseases of the brain which can include MS, Behcet’s disease, Sjogren’s syndrome, migraine, and small vessel atherosclerotic disease (Peterson et al. 2005). Conventional MRI sequences, such as spin-echo T2-weighted imaging (WI) and fluid attenuated inversion recovery technique (FLAIR) are widely used as diagnostic and prognostic tools in evaluating the SLE patient who is suspected of having CNS involvement (Baum et al. 1993; Peterson et al. 2005). Unenhanced T1-WI that can reveal hypointense lesions, a measure of chronic neurodegeneration, are usually normal (Peterson et al. 2005). In contrast, white matter hyperintensities on T2-WI are more common and diverse, most frequently seen in the frontal-parietal regions (Sibbitt et al. 1999). Group studies comparing patients with SLE and healthy controls typically show higher white matter lesion burden (Hachulla et al. 1998) among patients with SLE. Periventricular lesions have been particularly associated with the SLE and positive antiphospholipid antibodies (APLA) and are impossible to differentiate on MRI from MS or antiphospholipid antibody syndrome (APLS).

While the resolution of brain MRI is similar in these disorders, the few studies comparing lesion pathology among MS patients, secondary APLS, and SLE have shown that MS patients present with a higher burden of disease than APLS or SLE (Rovaris et al. 2000). T2-WI white matter hyperintensities increase with age in the general population and are also associated with hypertension, and it is not possible to differentiate white matter hyperintensities in SLE from other vasculopathies using conventional MRI. Conventional MRI techniques are also unable to provide full details about the chronicity of the lesions. Therefore, differentiation of acute lesions from old chronic lesions is a goal of future research. Presence of indistinct lesion borders, intermediate intensity of T2 lesions and gray matter lesions are all potential markers of acute pathology. The use of gadolinium enhanced T1-WI has also been shown to be helpful

in delineating active inflammatory lesions (Miller et al. 1992; Sibbitt et al. 1999). All this being said, one should bear in mind that a normal MRI scan is common in SLE when conventional MRI is employed, thus prompting research using other innovative MRI techniques to increase the sensitivity of MRI assessments.

Evolving brain imaging technologies may be able to improve the identification of subtle pathology in brain tissue that appears as normal on conventional brain MRI. Indeed, the identification of specific measures which show subtle brain pathology may help redefine NP-SLE by setting clearer imaging classification standards (Govoni et al. 2004). For example, identification and characterization of regional brain atrophy and microscopic changes with magnetization transfer imaging (MTI) could help in the evaluation of patients with suspected CNS involvement in SLE and in the understanding of the pathophysiology of the cognitive deficits in this population (see Govoni et al. 2004; Huizinga et al. 2001). As in MS (Filippi et al. 2000; Rovaris et al. 1999), several studies have shown MTI to be capable of detecting microscopic pathology in SLE (Bosma et al. 2000a, b; 2002; Rovaris et al. 2000). Bosma et al. (2000a, b) have applied MTI to the characterization of normal appearing brain tissue and the evolution of lesions in SLE. In one of their studies (Bosma et al. 2000a), they used MTI to study MS and SLE patients with and without a history of NP involvement. Magnetization transfer ratio histograms were abnormal in NP-SLE and MS patients, and the authors suggested that these manifestations in the cerebral white matter could include focal areas of demyelination, and/or vasculopathy. Additionally, they found that the MTR histogram parameters in chronic NP-SLE were very similar to those for MS.

Other innovative imaging techniques such as diffusion-weighted and -tensor imaging (DWI and DTI) have been applied to the study of the brain and spinal cord in SLE patients (Benedetti et al. 2007; Bosma et al. 2003). The possibility of being able to differentiate inflammatory lesions from ischemic damage with DWI is very promising (Peterson et al. 2003). DWI-DTI may be useful in differentiating ischemia associated with SLE-APS from inflammatory lesions and indeed from MS. A recent study used DTI to quantify the extent of occult injury of the cervical region of the spinal cord in 11 NP-SLE patients and 10 healthy controls (Benedetti et al. 2007). Only one patient had a single focal lesion of the cord whereas all had multiple brain lesions on conventional MRI scans. DTI revealed occult cord damage in NP-SLE, which might be secondary to Wallerian degeneration of long tract fibers passing through damaged areas of the brain. The Wallerian degeneration hypothesis is perhaps the most commonly proposed explanation of brain and spinal cord atrophy in the MS literature (Peterson et al. 2001; Trapp et al. 1999).

A number of studies utilized magnetic resonance spectroscopy (MRS) as a measure of neuronal metabolism to more clearly characterize cerebral disease in SLE from other autoimmune diseases (Friedman et al. 1998; Lim et al. 2000; Peterson et al. 2005; Sabet et al. 1998). *N*-acetyl aspartate (NAA), a marker of axonal loss, was reduced in normal appearing white and gray matter, as well as in lesions (Peterson et al. 2005). Choline metabolite was particularly elevated in NP-SLE patients with active lesions (Axford et al. 2001). In a more recent study, the choline/ creatine ratio from the normal appearing frontal white matter was elevated in a small sample of non-NP-SLE patients, and a significant relationship was present between this ratio and cognitive impairment in these patients (Kozora et al. 2005).

Functional imaging studies such as positron emission tomography (PET) have demonstrated a variety of abnormalities related to SLE. For example, several studies reported either glucose hypometabolism or hypoperfusion in the temporal, parietal, and frontal lobes (Stoppe et al. 1990; Lin et al. 1997; Kao et al. 1999). Weiner et al. (2000) found hypometabolism in similar areas including the frontal lobes, but little involvement of temporal areas. Using high resolution

instrumentation with SPECT, Kao et al. (1999) detected deficits in deeper brain structures such as the basal ganglia.

A few studies have attempted to detect associations between brain imaging findings and cognitive deficits in SLE patients. Kozora et al. (1998) examined ventricle-to-brain ratios and the total number of white matter lesions in 20 female patients with non-CNS-SLE. A comprehensive cognitive battery was used that included eight cognitive domains. Patients showed impairment in the domains of attention and learning. Only two borderline correlations were obtained between the cognitive variables of attention and fluency, and white matter lesions. Yet roughly 80% of the SLE patients had abnormal ventricle-to-brain ratios and 40% presented with white matter lesions.

The relationship between quantitative estimates of global brain damage based on MTI and neurologic, psychiatric, and cognitive functioning was investigated in a group of 24 females with NP-SLE (Bosma et al. 2002). Disease duration was also considered. The results of this study demonstrated that volumetric MTI parameters and brain atrophy reflected functionally relevant brain damage in SLE patients. Furthermore, the absence of a linear relationship between disease duration and results of volumetric MTI measures and atrophy suggested a complicated pattern of accumulating brain damage in patients with NP-SLE. Although this study demonstrated an association between global cerebral disease burden, as detected by MTI, and various measures of neurologic, psychiatric, and cognitive functions in NP-SLE, the only measure of cognitive function employed was a global measure of general intelligence. Nevertheless, the degree of association in this study is impressive, as the size of the correlations were moderate to large, as has been seen in the MS literature (Benedict et al. 2006b; Zivadinov and Bakshi 2004). More useful data may be derived with better validated cognitive batteries.

Finally, we should point out that some of the imaging studies have suggested transient processes and others indicate more permanent damage (Falcini et al. 1998; Nossent et al. 1991; Otte et al. 1997; Sibbitt et al. 1999). Nevertheless, none of these studies related functional or metabolic abnormalities to specific cognitive processes, only to general cognitive measures or neuropsychiatric problems such as major manifestations of confusion, seizures, psychosis, and depression (Kao et al. 1999). These studies, however, do provide data to support CNS pathophysiology in SLE patients with overt NP disturbances.

Cognitive Disorder in SLE

Impaired cognitive capacity has been reported in a large number of SLE studies using a variety of selection criteria and neuropsychological testing methods. The incidence of cognitive impairment has varied widely across studies, by as much as 21–80% (Ainala et al. 2001; Denburg et al. 1997a; Hanly et al. 1997), due to variation in testing methods, lack of proper control groups, differences in sample composition, and most important, variation in thresholds for positive tests. The lack of specificity in some of these studies is concerning. For example, in one study the frequency of cognitive impairment in SLE was 43%, but using the same criteria resulted in a false positive rate among healthy controls of 19% (Glanz et al. 1997a). Nevertheless, there is now agreement that a significant proportion of SLE patients are cognitively impaired, even in the absence of recent disease activity and overt neurologic or psychiatric signs of CNS involvement (Carbotte et al. 1986; Hanly et al. 1994, 1992; Hay et al. 1992; Leritz et al. 2002). The more recent opinions on the frequency of cognitive impairment in non-NP-SLE or NP-SLE who are free of acute illness range from 25–35% (Kozora et al. 2004, 2006). As would be expected, most studies conclude that neuropsychological impairment is more prominent in NP- or CNS-SLE (Denburg et al. 1987b; Hanly et al. 1992).

In a recent study comparing SLE patients and well-matched normal controls, NP-SLE patients were more cognitively impaired than non-NP patients (Loukkola et al. 2003), with impairment

most apparent on tests emphasizing psychomotor speed, complex attention, and memory, a pattern reminiscent of the MS literature (Benedict et al. 2002b). Cognitive impairment in SLE, even when early or subclinical, is a potentially important problem for scientific investigation. There may be a substantial proportion of SLE patients with subclinical or minimal cognitive impairment that represents the beginning of more profound CNS involvement.

It is important that factors such as physical disease activity, depression, and medication use be considered when studying the relationships between SLE and cognitive disturbances. The effects of psychological variables on cognition have been reported in a number of previous studies of SLE patients with overt CNS disease (Denburg et al. 1987b; Hay et al. 1992, 1994; Wekking et al. 1991). However, most studies fail to find that depression or anxiety are primary causes of cognitive impairment in SLE (Denburg et al. 1987b; Glanz et al. 1997a; Kozora et al. 1996). Additionally, studies have rarely found an association between cognitive impairment and current depressive symptoms or corticosteroid use (Glanz et al. 1997a; Shucard et al. 2004b), and no reliable association between cognitive performance, and SLE and disease activity in other organ systems (Carbotte et al. 1995; Denburg et al. 1987a, b, 1994; Shucard et al. 2004b). Corticosteroids are commonly used to treat acute inflammation in SLE. As noted above, most studies have found little association between steroid treatment and cognitive impairment in SLE (Ginsburg et al. 1992; Glanz et al. 1997b), although contradictory findings have been reported (Hanly et al. 1992). There are some data to suggest that steroid treatment can improve cognitive performance (Denburg et al. 1994). Altogether, these data suggest that cerebral pathology is the critical factor in the development of cognitive impairment in SLE, and that indirect effects related to the presence or severity of symptoms due to organ involvement or to factors such as depression and corticosteroid use are less important in the measurement of neuropsychological morbidity.

Although many previous studies of cognitive impairment in SLE do not reveal a specific cognitive profile, they do suggest that the deficits seen in SLE most typically involve attention, free recall of recently-learned information, information processing speed and working memory, and spatial processing. Based on these and similar observations, cognitive performance in SLE has been regarded by some as reminiscent of the so-called “subcortical” pattern, as seen in Huntington’s disease compared to a more cortical pattern seen in Alzheimer’s disease (Leritz et al. 2000). Kozora et al. (1996) compared non-NP SLE patients to a rheumatoid arthritis (RA) group and a healthy control group. They found that differences in cognitive function were present between the groups for the domain of learning efficiency in which 33% of SLE and 14% of RA patients had difficulty encoding material, suggesting the possibility of memory impairment. The investigators noted that the deficit was related more to acquisition than retrieval.

Denburg et al. (1987b, 1997b) in two separate studies, found that non-NP SLE patients failed tasks that involved visual/spatial memory, auditory/verbal learning, psychomotor speed, and cognitive flexibility. In the Leritz et al. (2000) study, 11 items from the Folstein Mini-Mental State Exam (MMSE) classified 95% of SLE patients as having “subcortical” dysfunction. Among those abilities that were affected were attention, working memory, and mental tracking. These processes have been associated with neural circuits that involve connections between subcortical structures and prefrontal cortex, as was demonstrated in some of the brain imaging studies reviewed above. In a recent study by our group (Shucard et al. 2004a) we used the Paced Auditory Serial Addition Test (PASAT; Gronwall 1977) to explore processing speed and working memory deficits in SLE patients without overt CNS involvement. Alternative PASAT scoring procedures were used (Fisk and Archibald 2001; Snyder et al. 2001) that isolate more specifically the working memory and processing speed components of the test. While the performance of SLE patients and controls did not differ on the traditional PASAT scores, their performance was significantly poorer than controls for the alternative scoring measures,

reflecting subtle but significant processing speed and working memory deficits in this group. Importantly, our findings could not be attributed to disease activity, disease duration, depression, fatigue, or corticosteroid use, demonstrating that CNS injury could be present in patients with SLE who did not have overt CNS disturbances.

Association with Inflammatory and Immunologic Markers

Chronic inflammation is thought to be a key factor in SLE that contributes to the development of the vasculopathy seen in this disease. The precise mechanisms are not known; however, it is postulated that autoimmune complexes attack the endothelial walls and other components of the vasculature causing an inflammatory response that, when chronic, leads to a cascade of events such as scarring, autoimmune deposits, vascular stiffness, hypertension, and risk for arterial hemorrhage and embolic occlusion as well as further damage to endothelial walls (Kao et al. 2003; Selzer et al. 2001; Verma et al. 2003). There is supportive evidence of this notion of vascular injury in SLE. For example, higher rates of aortic stiffness, myocardial infarction, and stroke have been reported in the setting of large-vessel disease (Fluture et al. 2003; Manzi et al. 1997; Mok et al. 2001; Roman et al. 2003; Selzer et al. 2001). Also, there is evidence that large vessel disease in SLE may begin as a microvascular process. Thirty-nine percent of SLE patients with associated antiphospholipid syndrome showed increased presence of microemboli on Doppler readings (Rademacher et al. 1999).

Because of the evidence of vascular involvement and the chronic inflammatory nature of SLE, there has been interest in measuring and predicting vasculopathy and disease activity in SLE. It appears that C-reactive protein (CRP), a serum inflammatory marker, is highly sensitive to the inflammatory response related to cell damage, including that of endothelial cells (Verma et al. 2003). CRP levels in SLE patients have been positively associated with other markers of inflammatory disease such as fibrinogen (Selzer et al. 2001), and low-density lipoprotein and lipid hydroperoxide levels (Nuttall et al. 2003). Other research has shown involvement of inflammatory processes and vasculitic events in the pathogenesis of SLE (Mochizuki et al. 1999).

Relevant to this review and its focus on cognition, studies have shown relationships between elevated CRP and depression (Danner et al. 2003), and elevated CRP and cognitive decline in healthy individuals (Schmidt et al. 2002; Teunissen et al. 2003). As discussed, the cognitive deficits seen in SLE are presumed to involve abnormalities in subcortical white matter thereby causing disruption of subcortical–cortical neural circuits. Based on the data from previous studies of inflammation and pathology in SLE, and the sensitivity of CRP as a marker of inflammatory processes, our laboratory investigated the possible relationship between cognitive deficits (working memory/processing speed) in SLE and CRP levels (Shucard et al. 2007). The findings showed that compared to patients with SLE with no detectable CRP, the patients with elevated CRP performed more poorly on cognitive testing, suggesting that CRP may be a sensitive marker of minimal cognitive disturbance in SLE. This was the first study, to our knowledge, to link CRP levels with processing speed/working memory deficits in SLE.

Cognitive impairment has also been linked with the influence of antibodies against brain antigens which may be collected from the serum in patients with SLE. Consistent with the hypothesis that neuropsychological impairment in SLE is at least partly related to the effects of antibodies to brain tissue, Denburg et al. (1987a, 1988) have shown that positive brain cross-reactive lymphocytotoxic antibody and IgG anti-neuronal antibody tests are associated with greater cognitive impairment in NP-SLE. Plasma levels of the cytokine interleukin-6 (IL-6) and cognitive impairment were also evaluated in non-CNS SLE by Kozora et al (2001). The patients were impaired relative to controls on tests emphasizing processing speed and new learning. Regression analysis showed that significant variance in cognitive performance was

accounted for by the IL-6 after controlling for the effects of depression and corticosteroid treatment. Of course these few studies are only the beginning of research into the complex relationships between cytokine activity and neuropsychological impairment in SLE.

Analysis of Effect Size Across Cognitive Domains in SLE

We now turn our attention to the concept of effect size across five general cognitive domains. Our emphasis is on the Cohen *D* statistic (Cohen 1988), an easily understood statistic that represents the difference between SLE and control means, divided by the pooled SD. The literature provides too few studies to support a formal meta-analysis. Nevertheless, examining effects across the available studies may shed light on the degree and quality of cognitive impairment in SLE, and permit gross comparison with MS. To be included in this section, studies must have met three criteria: (a) SLE sample $n \geq 20$; (b) healthy control group with $n \geq 10$ and matched on demographics or with statistical control for the same; and (c) reproducible testing procedure, if not a standardized test battery the experimental tasks are clearly described so that the study could be replicated. Studies were included regardless of whether the patients were described as NP-SLE, CNS-SLE, or non-CNS-SLE. However, studies using NP- or CNS-SLE patients were only considered if overt neurological involvement such as focal neurological syndromes caused by stroke or other focal brain injury were excluded. A surprisingly few number of studies met these standards for inclusion.

The oft cited study of Wekking et al. (1991) exemplifies the last point. Twenty SLE patients were studied, nine of whom were designated CNS-SLE and 11 were designated “without CNS-SLE.” Three within the former group were labeled “organic brain syndrome,” one of whom “underwent a brain infarct.” The reader was not informed as to how organic brain syndrome was specifically defined, or in what part of the brain the infarct was found. Therefore, even if the groups were combined, the study could be misleading due to the inclusion of these brain-injured patients. In contrast, the more recent study of Emori et al. (2005) serves as an example of what is in our view a more valid sample composition. They studied a small sample of 21 SLE patients, but excluded those with brain MRI abnormal signal intensities of two mm or greater or with evidence of “obvious atrophy.” It could be argued that the cut-off of two mm is too stringent, but at least these authors attempted to exclude patients with focal strokes via brain imaging standards. The patients were compared with 17 healthy controls matched on age and gender composition. Unfortunately, this article did not include the SDs of mean cognitive test scores which would have enabled effect size calculations as below. ANOVAs did reveal impairments on the Rey Auditory Verbal Learning Test (Rey 1964) and the Trail Making Test (TMT; Reitan 1958).

Finally, in order to avoid test selection bias we included studies assessing any of five general cognitive domains: language, spatial processing, episodic memory, processing speed or working memory, and higher executive function. We acknowledge that there are many tests that involve more than one modality. Because the Wechsler intelligence scales (Wechsler 1997) are often regarded as less sensitive to cerebral disease than most other neuropsychological tests, they were not included in the effect size calculations, except the Digit-Symbol subtest due to its similarity to the Symbol Digit Modalities Test (SDMT; Smith 1982), which has established sensitivity in MS (Benedict et al. 2006c; Parmenter et al. 2007c) as will be seen below. In the domain of language we included tests emphasizing the rate or fluency of oral/verbal expression, such as the Controlled Oral Word Association Test (COWAT; Benton and Hamsher 1989). Spatial processing was conceptualized as a very general category encompassing perceptive, constructive and speed aspects of visual/spatial test performance. Commonly-used tests emphasizing attention such as the Paced Auditory Serial Addition Test (PASAT) and the Trail Making Test (TMT) require both rapid responding and working memory, and thus we consolidated our review of such tests into a single domain.

Finally, by executive function, we refer to tests which emphasize conceptual reasoning and problem-solving over that of speed and memory. Many cognitive tests provide multiple outcome measures. We accepted up to only two scores from each test and emphasized commonly used measures such as total learning and delayed recall from traditional word-list learning tests. Below we describe the studies in chronological sequence, corresponding to the summary statistics in Table 2.

Perhaps the most comprehensive neuropsychological study ever conducted with patients with SLE was one of the first (Denburg et al. 1987b). Neuropsychological tests spanning multiple domains were administered to 86 SLE patients and 35 controls, closely matched on age and education. The patients were categorized into three groups: active NP-SLE, inactive NP-SLE, and non-NP-SLE. Unfortunately, the NP-SLE groups included patients with abnormal EEGs, CSF analysis, angiograms, or brain imaging. Moreover, the statistical analysis emphasized differences between NP- and non-NP patients. As would be expected, significant differences emerged between NP- and non-NP-SLE, and we are left wondering if the deficits may have been related to focal strokes or some other, more occult pathology. Nevertheless, the authors provide a rich data table which includes 38 cognitive variables. Included in Table 2 are some of the effect sizes pertaining to the non-NP SLE patients. While the ANOVAs did not focus on non-NP-SLE patients versus controls, it can be seen that there were some effects of 0.3, and after the composition of domain summary statistics, some impairment was seen in the non-NP-SLE group, leading the authors to argue for the presence of “subclinical CNS involvement in these patients.”

The question of whether cognitive impairment occurs in “inactive” SLE was investigated in 58 patients and 47 controls (Glanz et al. 1997b). Unfortunately, the SLE group was significantly older than the controls, and thus the effects depicted in Table 2 should be interpreted cautiously. The statistical analysis emphasized the frequency of cognitive impairment using age-adjusted, manual norms. Whereas 19% of controls were impaired, 43% of patients with SLE were impaired. ANCOVAs covarying for the effects of age and IQ showed significant impairment on summary scores measuring auditory/verbal and visual/ spatial memory as well as measures of psychomotor speed and cognitive flexibility.

Our group (Shucard et al. 2004a) examined PASAT performance in 33 patients with SLE screened for focal neurological disorder. Patients with SLE performed more poorly than controls, especially when the primary outcome was the percentage of chunking responses, a newly developed scoring procedure that more accurately reflects working memory on this test (Fisk and Archibald 2001; Snyder et al. 2001). Further, we found that these deficits could not be accounted for by disease activity, disease duration, depression, fatigue, or corticosteroid use.

The reliability and validity of the ACR-SLE battery was investigated in an elegant study by Kozora et al. (2004). The participants were carefully assessed and screened for a wide range of neurological complications using questionnaires and standardized interview techniques. The NP-SLE group included 10% with stroke, movement disorder, or meningitis and because there were no imaging results to exclude focal brain lesions, or effect size, analysis is limited to the 22 non-NP-SLE patients. The controls were closely matched on demographic characteristics. Most prominent impairment was found on those tests emphasizing processing speed, working memory and decision making speed. The test battery demonstrated test-retest reliability and was highly correlated with a more comprehensive battery of tests.

Finally, Glanz et al. (2005) recently compared patients with SLE and controls using a large test battery designed to distinguish left-and right-hemisphere functions. The patients were recruited from an outpatient center, and individuals with discernible cerebrovascular disease

were excluded. Significant effects were discovered on the Digit Symbol subtest from the WAIS-R, the Logical Memory and Visual Reproduction subtests from the Wechsler Memory Scale, 3rd edition (WMS-III) and the TMT. Because impairments based on a categorization method were most prominent on tests of verbal processing, and cerebrovascular disease was excluded, the authors opined that the data suggested the presence of regional (i.e., left hemisphere) brain injury. Our own analysis of effect size, however, does not support this conclusion.

Overall, inspection of Table 2 leads to the conclusion that when patients with SLE without prominent cerebrovascular disease or focal cerebral infarction are compared to healthy controls, the degree of impairment, as reflected by the mean effect size within each domain, is in the range of $D=0.2$ to 0.5 . The impairment is most apparent on tests emphasizing visual/spatial learning as well as processing speed and/or working memory (Fig. 1). As will be seen below, this pattern of impairment is reminiscent of neuropsychological deficit in MS.

Comparison with MS

Early pathology studies examining the location of MS demyelinating plaques showed that both the white matter and the cortex are affected (Brownell and Hughes 1962). Nevertheless, MS has long been regarded as a white matter disease. In the traditional view, neurological defects are the result of demyelination which disrupts the propagation of action potentials along axons. MS-associated cognitive disorder often involves slowed processing speed, hence the classic designation of MS as a so-called white matter dementia (Filley et al. 1989; Swirsky-Sacchetti et al. 1992). However, the role of cortical and deep gray matter pathology is increasingly appreciated (Cifelli et al. 2002; Kidd et al. 1999; Kutzelnigg et al. 2005). In addition to demyelination, axonal transection, dendritic transection, and apoptosis are believed to contribute to cognitive and neurological deficits (Peterson et al. 2001). Tissue destruction is appreciated in the cortical gray matter (Cercignani et al. 2000) and is associated with clinical status (Chard et al. 2002). There is debate about the extent to which gray matter pathology is similar to that in the white matter (Kutzelnigg et al. 2005), is secondary to axonal injury in the white matter (Trapp et al. 1998), or represents an entirely independent degenerative process. Recent data indicate that cortical demyelination is not correlated with the extent of demyelinating lesions in the white matter among patients with chronic, progressive MS course (Bo et al. 2007). Whatever the process, observations suggest that once a certain threshold is reached, a cascade of neurodegeneration ensues (Hauser et al. 2006), so that there appear to be two overlapping pathologic aspects of the disease: inflammatory and neurodegenerative (Pirko et al. 2007).

Roughly half of all MS patients are cognitively impaired (Beatty et al. 1989; Fischer 1988; Rao et al. 1993, 1991a), although the incidence is somewhat higher in clinical samples (Benedict et al. 2006c). Two early studies (Heaton 1985; Rao et al. 1991a) revealed that as a group, patients with MS are most often impaired on neuropsychological tests that emphasize processing speed, working memory, new learning, and episodic memory. The finding of impaired cognitive performance in MS has been replicated many times (Beatty et al. 1989; Fischer 1988; Rao et al. 1993). Other cognitive impairments have been described, involving such domains as spatial processing (Vleugels et al. 2000), verbal fluency (Beatty 2002), and higher executive function (Arnett et al. 1997; Beatty et al. 1995; Beatty and Monson 1996; Foong et al. 1997). Neuropsychological defects are associated with progressive more than relapsing disease course (Beatty et al. 1988) and MRI evidence of lesion burden and brain atrophy (Amato et al. 2004; Benedict et al. 2002a, 2004a; Christodoulou et al. 2003; Rao et al. 1989a). Abnormal neuropsychological testing also predicts failures in activities of daily living such as automobile driving (Schultheis et al. 2001, 2002), employment (Benedict et al. 2005;

Rao et al. 1991b), success in rehabilitation (Langdon and Thompson 1999), and social skills (Arnett et al. 1994; Benedict et al. 2001; Knight et al. 1997).

Episodic memory may be the cognitive domain most frequently investigated in patients with MS. Most studies reveal that patients with MS are impaired in their ability to explicitly learn and subsequently recall new material, regardless of whether the material is verbal or visual (Amato et al. 1995; Beatty et al. 1989; Camp et al. 1999; Grafman et al. 1991; Minden 1990; Rao et al. 1984; Ryan et al. 1996). Two lines of research have been particularly influential in this regard. First, DeLuca et al. (1994) found that when patients with MS are confronted with a word-list learning task, they recalled less information than controls after the first stimulus presentation and benefited less from repeated exposures. However, once the patients were permitted extra trials to attain the same level of initial learning, delayed recall was intact. These data showed that much of the memory deficit in patients with MS can be accounted for by poor encoding. Other research from Rao et al. (1989b) has emphasized the discrepancy between free recall and recognition memory performance, the latter being preserved in most studies. Recognition memory is indeed most often spared or less pronounced than deficits in free recall (Thornton 1997; Wishart 1997). These data highlight the retrieval aspects of memory disorder in MS.

Deficits in information processing speed are well documented in MS (Archibald and Fisk 2000; D'Esposito et al. 1996; DeLuca et al. 1993, 2004; Demaree et al. 1999; Fisk and Archibald 2001; Kujala 1994; Litvan et al. 1988; Parmenter et al. 2006; Snyder et al. 2001). Patients with MS typically fail tests that emphasize rapid responding or working memory, and it appears that deficiency in these areas are strongly interrelated (Parmenter et al. 2006, 2007a). The clinical tests recommended to assess this domain by both the Rao (Rao 1990, 1992; Rao et al. 1991a) and MACFIMS (Benedict et al. 2002b) groups are the Paced Auditory Serial Addition Test (PASAT) and the Symbol Digit Modalities Test (SDMT). The SDMT has proven to be the more sensitive (Parmenter et al. 2007c) and reliable (Benedict 2005) in recent research. The SDMT is a visual test, and it is possible that its sensitivity is due, in part, to afferent or sensory dysfunction in MS. Recently, our group, using a N-back task, reported interesting findings that pertain to processing speed and working memory in MS (Parmenter et al. 2006). This task allowed us to parse information processing speed and working memory and we showed significant impairment of both information processing speed and working memory in patients with relapsing remitting MS.

As may be apparent from the above discussion, neuropsychological functioning in MS patients has been more thoroughly investigated than in SLE. However, these diseases have much in common. First, both affect other organs or the CNS in regions that have little direct impact on mental abilities, such as the spinal cord. Thus, some patients with each disorder are completely free of neuropsychological compromise. Second, both are immunological disorders, at least as broadly defined. Third, both are inflammatory disorders and involve lesions of the cerebral white matter. Fourth, the disease course of MS and SLE involves periods of relative stability or quiescence, and more acute phases often referred to as relapses or attacks. Fifth, when the brain is involved, the injury is usually widespread rather than focal. Finally, in both populations the incidence and nature of cognitive impairment has been debated, leading to consensus papers pertaining to cognitive disorders and recommended testing batteries (Benedict et al. 2002b; Kozora et al. 2004; Peyser et al. 1990). The modified McDonald criteria may provide the best combination to date of sensitivity and specificity for an accurate diagnosis of MS (Polman et al. 2005). Lesion distribution could be helpful in differentiating the two diseases, since vascular lesions predominate in SLE and periventricular and especially corpus callosum demyelinating lesions are more common in MS (Zivadinov and Bakshi 2004). Nevertheless, we believe that MS provides a useful comparison for the SLE literature.

In 2002, a consensus opinion manuscript (Benedict et al. 2002b) proposed what has come to be called the Minimal Assessment of Cognitive Function in MS (MACFIMS). Since then, we and others have shown the tests to be reliable (Benedict 2005), predictive of multiple forms of brain pathology (Benedict et al. 2006b; Christodoulou et al. 2003; Tekok-Kilic et al. 2007), and associated with vocational disability (Benedict et al. 2005; Parmenter et al. 2007b). The battery includes the following tests: Controlled Oral Word Association Test (COWAT; Benton et al. 1994), Judgment of Line Orientation Test (JLO; Benton et al. 1994), California Verbal Learning Test, second edition (CVLT2; Delis et al. 2000), Brief Visuospatial Memory Test-Revised (BVMTR; Benedict 1997), Paced Auditory Serial Addition Test (PASAT; Gronwall 1977), Symbol Digit Modalities Test (SDMT; Smith 1982), and the Delis-Kaplan Executive Function System Sorting Test (DKEFS; Delis et al. 2001). Most often, the Total Learning and Delayed Recall indices from the CVLT2 and BVMTR are emphasized. The consensus panel also recommended Rao's adaptations (Rao 1990) of the PASAT and SDMT.

We (Benedict et al. 2006c) recently investigated the validity of the MACFIMS in a prospective sample of 291 MS patients and 56 controls, matched on age, education, gender and race. Patients were screened for prior neurological and psychiatric disorder and had not undergone relapse within four weeks of testing. Global impairment was defined as a defect (z of normal ≤ 1.5) on two or more tests. ANOVAs showed that all tests discriminated the groups ($p < 0.01$). Using this standard, the frequency of cognitive impairment was 59.5%. The most sensitive test in the MACFIMS battery was the SDMT (51.9% impaired). In addition, SDMT predicts vocational outcomes more than quantified neurological exams and a range of other clinical parameters (Benedict et al. 2005).

Figure 1 shows the mean effect size across six domains of cognitive function gleaned from the Benedict et al. 2006b study. It should be noted that the profile is very similar to the seminal work of Rao et al. (1991a,b) in MS cognitive disorder. Also presented are the mean SLE effect sizes taken from Table 1. There is a common pattern wherein processing speed and visual/spatial learning are the most significant domains in both diseases.

Finally, there are additional comparison of MS and SLE in the area of structural brain imaging. In MS, many early studies showed a significant relationship between lesion volume and cognitive impairment. More recently, measures reflecting brain atrophy have been more strongly correlated with cognitive impairments, such as reduced whole brain volume (Zivadinov et al. 2001), enlargement of the ventricles (Benedict et al. 2004a, c; Bermel et al. 2002; Christodoulou et al. 2003), and reduction in cortical volume (Amato et al. 2004; Benedict et al. 2006b). The clinical relevance of regional cortical volume is beginning to be explored (Morgen et al. 2006; Prinster et al. 2006; Sepulcre et al. 2006; Tekok-Kilic et al. 2007).

Both MS and SLE often involve either demyelinating (in MS) or ischemic (SLE) lesions of the white matter (Fig. 2). As noted above, the cerebral pathology of SLE appears to arise from a combination of the primary effects of autoantibody activity, and the secondary effects from vasculopathy, and in turn small vessel disease. Thus, there is a higher frequency of cerebral infarction involving the gray and white matter in SLE than in MS, although there is growing evidence that SLE is associated with a destructive brain process that may contribute to occult axonal damage, and in some cases brain atrophy (Chinn et al. 1997). As noted above, recent developments of MRI technology have enabled the detection of subtle breakdown of neural tissue which is not discernible to gross inspection of even high-field images. While there are far fewer studies investigating correlation between brain MRI and cognitive impairment in SLE, the findings to date show significant association with ventricular enlargement and subtle changes in the normal appearing white matter. Therefore, the literature is now suggesting that when investigation is limited to NP-SLE, the degree of association between MS and SLE is striking.

Conclusions and Future Directions

In this review we have attempted to summarize the literature about cognitive impairment in SLE, and to contrast these studies with the MS neuropsychological literature. Both diseases are associated with cognitive disorder, and both affect the cerebral white matter. Unlike MS, SLE is characterized by multisystem organ involvement and, as a result, there is a much wider range of symptoms and tissue injury.

Most prevalence estimates of cognitive impairment in MS approximate 50%, and there is consensus in the literature on this value. Samples derived from community advertisement are somewhat lower (Rao et al. 1991a), whereas consecutive clinic attendees are more often impaired (Benedict et al. 2006c). In our recent study of 291 MS patients, 59.5% were impaired using the same decision rules as in the study of Rao et al. (1991a) of 100 MS patients. Of equal importance was the nearly overlapping cognitive profile, with tests emphasizing processing speed, working memory, and episodic recall showing greater sensitivity. There does not appear to be any published SLE studies utilizing a community volunteer sample. When the available studies have focused on either inactive NP-SLE, NP-SLE patients without discernible stroke, or patients without a history of CNS involvement, the prevalence of neuropsychological deficits has been somewhat lower than in MS, in the vicinity of 25–35%. It is reasonable to assume that the frequency of cognitive impairment among SLE patients with stroke or other CNS injuries is bound to be considerably higher.

Nevertheless, inspection of Fig. 1 suggests that the profile of neuropsychological impairment is similar between MS and SLE populations. We propose that the similarity in profiles reflects underlying diffuse, white matter pathology found in both disorders. The greater impairment seen in MS may reflect the degree of white matter damage, or the increasing involvement of cortical and deep gray matter structures that arises in those patients showing chronic progression of neurological disability and brain atrophy. In Fig. 2 we present sample brain MRI axial FLAIR scans from patients with the same disease duration and demographics, illustrates the greater atrophy and lesion burden in MS. Evidence for brain atrophy is rarer in SLE, but when seen seems to be strongly correlated with cognitive impairment (Bosma et al. 2002). In contrast, brain atrophy in MS can be severe (Benedict et al. 2006b;Carone et al. 2006;Ramasamy et al. 2007), and when seen it often correlates with cortical and subcortical dementia (Benedict and Bobholz 2007).

Both SLE and MS are associated with MRI evidence of neuronal tissue damage in the cerebral white matter that appears normal on conventional MRI. In one study comparing these diseases, the degree of MTR abnormality was roughly the same between MS and NP-SLE. This finding suggests that the neuropsychological presentation of NP-SLE (without focal brain injury) and early MS (without prominent brain atrophy) might be very similar, characterized by slowing on cognitive tests, reduction in working memory capacity, and failure on some tests of spatial (or novel) learning and episodic memory. One heuristic concept may then be that the cognitive presentation for these diseases begins in a similar manner, due to the early involvement of the cerebral white matter. While the cause of this damage may be different across MS and SLE, the clinical result is more or less the same—slowing of transmission between various cortical regions and between cortical and deep gray matter nuclei causes slowed mental processing. Later, the course of these illnesses diverge, with the development of gray matter atrophy in MS, and increasing risk of focal infarction in SLE.

Another point of divergence in the neuropsychology of MS and SLE concerns the prominent role of autoimmunity in the latter. Studies investigating the contribution of systemic inflammation, anti-neuronal antibodies and cytokine activity have shown fairly consistent linear relationships with cognitive impairment. In SLE, there is good evidence that elevated

CRP levels have an adverse impact on cognitive functioning. In addition, IL-6 and multiple anti-neuronal antibodies are known to contribute to neuropsychological test performance. The nature of the impairment is often related to slowed information processing. Presently, there is no means to disentangle the effects of these factors and vascular causes of occult white-matter tissue damage.

We have found this review of the SLE literature difficult because most of the studies that included NP-SLE patients failed to exclude patients with “organic brain syndrome,” history of clinical stroke, and alike, or they included only non NP-SLE patients, thus, potentially omitting patients that could be important to the understanding of cognitive function in SLE. SLE is a disease in which multiple organ systems other than the CNS may be involved, and it is believed that some patients have no CNS involvement, depending on how this is measured. Without neuropsychological assessment or quantitative imaging, the conclusion that there is no CNS involvement may not be valid. We propose that, rather than dividing SLE patients into NP or non-NP groups, it may be more useful to separate patients into those with or without identifiable brain lesions such as cerebral infarction. Patients with NP syndromes other than such overt ones should be included when the purpose of research is to study the effects of subtle brain disease which presumably exists in many patients, with and without overt CNS symptoms. More recently, some studies of cognitive function in SLE have been moving in the direction of only excluding patients with marked cerebral pathology, which may serve as a useful direction for future studies of cognitive function in SLE.

Some patients with MS and SLE are cognitively impaired and because cognitive impairment can have marked impact on activities of daily living, work capacity, and compliance with medical therapy, there is a need to identify affected patients. As in MS, there is now a consensus neuropsychological battery for patients with SLE and some authors have suggested that routine cognitive testing of patients with SLE be considered (Newman 1993). Since the ACR-SLE battery requires only one-hour to administer, it is conceivable that it could be used routinely with SLE patients. However, it can be debated whether a routine neuropsychological examination is indicated in a disease in which only a minority may be impaired, raising the question of whether a brief screening test may be helpful in this population. In MS, questionnaire-based methods and single, sensitive cognitive tests have been proposed for this purpose. The MS Neuropsychological Screening Questionnaire (MSNQ) has shown some promise in identifying patients at higher risk for neuropsychological and neuropsychiatric disorder (Benedict et al. 2004b), although only the informant or caregiver-report version is sufficiently sensitive and specific for targeting patients with cognitive impairment (Benedict et al. 2004b; O’Brien et al. 2007). Alternatively, single tests, which are easily administered and have strong concurrent validity such as the SDMT have been proposed to screen for cognitive impairment in patients with MS (DeLoire et al. 2006; Parmenter et al. 2007c). This latter approach also has potential for SLE given that similar tests also have high sensitivity with the disease.

Abbreviations

ACR	American College of Rheumatology
APLA	antiphospholipid antibodies
APLS	antiphospholipid antibody syndrome
BVMTR	

	Brief Visuospatial Memory Test-Revised
COWAT	Controlled Oral Word Association Test
CND	central nervous system
CRP	C-reactive protein
CVLT2	California Verbal Learning Test, second edition
DKEFS	Delis–Kaplan Executive Function System Sorting Test
DTI	diffusion tensor imaging
DWI	diffusion weighted imaging
FLAIR	fluid attenuated inversion recovery technique
IL-6	interleukin-6
JLO	Judgment of Line Orientation Test
MACFIMS	Minimal Assessment of Cognitive Function in MS
MRI	magnetic resonance imaging
MRS	magnetic resonance spectroscopy
MS	multiple sclerosis
MTI	magnetization transfer imaging
MTR	magnetization transfer ratio
NAA	<i>N</i> -acetyl aspartate
NP	neuropsychiatric
PASAT	Paced Auditory Serial Addition Test

RA	rheumatoid arthritis
SDMT	Symbol Digit Modalities Test
SLE	systemic lupus erythematosus
TMT	Trail Making Test
WI	weighted imaging
WMS-III	Wechsler Memory Scale, 3rd edition

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Fig. 1.
Comparison of effect sizes between MS and SLE

Multiple Sclerosis**SLE** **Fig. 2.**

Displayed are axial FLAIR images [TE 121.858, TR 8502, TI 2100, FLIP 90, ETL 1, thickness 3.0, Gap 0, Matrix 256×192] obtained on three Tesla scanner in a 37-year-old patient with multiple sclerosis (MS; *left*; disease duration 8 years) and in a 37-year-old patient with systemic lupus erythematosus (SLE) (*right*) (disease duration nine years). The MS patient's brain is more atrophic. There is also higher white matter hyperintense lesion volume in periventricular (*upper row*) and cortical (*lower row*) brain regions in MS (38,479.9 mm³) compared to the patient with SLE (1,136.4 mm³)

Table 1

The neuropsychiatric syndromes in SLE according to the American College of Rheumatology (1999) nomenclature

Central Nervous System	Peripheral Nervous System
Aseptic meningitis	Acute inflammatory demyelinating polyradiculo-neuropathy (Guillain–Barre syndrome)
Cerebrovascular disease	Autonomic disorder
Demyelinating syndrome	Mononeuropathy, single/multiplex
Headache	Myasthenia Gravis
Movement disorder (chorea)	Neuropathy, cranial (usually optic neuritis)
Myelopathy (Transverse Myelitis)	Plexopathy
Seizure disorder	Polyneuropathy
Acute confusional state	
Anxiety disorder	
Cognitive dysfunction	
Mood disorder	
Psychosis	

Table 2

Effect sizes in SLE studies

Author	Number	SLE sample	Language	Spatial processing	Auditory/verbal episodic memory	Visual/spatial episodic memory	Processing speed, complex attention, working memory	Executive function
Denburg et al. 1987a, b	41	Non-NP	COWAT 0.1 Category FI 0.2	CFT-C 0.3 Design FI Free 0.1 Design FI Fixed -0.1	RAVLT-TL -0.2 RAVLT-DR -0.2 WMS-LM1 0.2 WMS-LM2 0.3	CFT-DR 0.3 WMS-VR1 0.0 WMS-VR2 0.3	TMT-A -0.2 TMT-B 0.1 Stroop 0.2	N/A
Glanz et al. 1997a, b	58	Mixed	Letter FI 0.4 Category FI 0.4	CFT-C 0.8	RAVLT-TL 0.8 RAVLT-DR 0.6 WMS-LM1 0.6 WMS-LM2 0.6	CFT-DR 0.8 WMS-VR1 1.2 WMS-VR2 1.1	TMT-A 1.0 TMT-B 0.8 Stroop 0.8 DST 1.0	N/A
Monastero 2001	51	Non-NP	COWAT 0.6	CFT-C 0.9	RAVLT-TL 1.6 RAVLT-DR 0.5	CFT-DR 1.6	TMT-A 0.0 TMT-B 0.0	RPM 0.1
Loukkola et al. 2003	31	Non-NP	COWAT 0.0 Category FI 0.4 BNT -0.3	3D-Drawing -0.1	CVLT-TL 0.1 CVLT-DR 0.2 WMSR-LM1 0.3 WMSR-LM2 0.2	WMSR-VR1 0.2 WMSR-VR2 0.0	TMT-A -0.2 TMT-B 0.1 Stroop 0.2	WCST-PR 0.6 ^a WCST-C 0.3
Shucard et al. 2004a, b	33	Mixed	N/A	N/A	N/A	N/A	PASAT-2.4 0.8 ^a	N/A
Kozora et al. 2004	22	Non-NP	COWAT 0.5	Design FI -0.2	CVLT-TL 0.3 CVLT-DR 0.0	CFT-DR 0.3	PASAT-2.0 1.0 ^a TMT-A 0.9 TMT-B 1.0 Stroop 0.7 DST 0.8	Category Test 0.4
Glanz et al. 2005	50	Mixed	COWAT 0.1 Category FI -0.1	CFT-C 0.2 Design FI Free 0.1 Design FI	CVLT-TL 0.0 CVLT-DR 0.0	CFT-DR 0.4 WMS-VR1 0.4	PASAT 0.8 TMT-A 0.5 TMT-B 0.5 Stroop 0.4 DST 0.7	N/A

Author	Number	SLE sample	Language	Spatial processing	Auditory/verbal episodic memory	Visual/spatial episodic memory	Processing speed, complex attention, working memory	Executive function
			BNT 0.3	Fixed 0.1	WMSR-LM1 0.5 WMSR-LM2 0.6	WMS-VR2 0.5		

Studies are presented in chronological sequence.

Inclusion requirements are $n > 25$, demographically matched healthy controls, data presented allowing calculation of Cohen's d effect size.

Effect sizes always presented as NC-SLE direction.

BNT Boston Naming Test, *CFT* Complex Figure Test, *COWAT* Controlled Oral Word Association Test, *CVLT* California Verbal Learning Test, *DST* Digit-Symbol subtest of the Wechsler scales, *FI* fluency, *LM* logical memory, *NP* neuropsychiatric, *PASAT* Paced Auditory Serial Addition Test, *RAVLT* Rey Auditory Verbal Learning Test, *RPM* Raven's progressive matrices, *Stroop* Stroop Color/Word Test, conflict trial, *TMT* Trail Making Test, *VR* visual reproduction, *WCST* Wisconsin Card Sorting Test, *WMS* Wechsler Memory Scale

^aSignifies group difference reported as statistically significant at $p < 0.05$, however, if there is no designation there may be no significance or there was no direct statistical comparison.