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Inflammatory and hormonal measures predict neuropsychological functioning in systemic lupus erythematosus and rheumatoid arthritis patients

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Abstract

Abnormalities of inflammatory and hormonal measures are common in SLE patients. Although cognitive dysfunction has been documented in SLE patients, the biological mechanism of these deficits has not been clarified. The goal of this study was to explore the relationship between inflammatory and hormonal activity and measures of learning, fluency, and attention in systemic lupus erythematosus patients without neuropsychiatric symptoms (non-CNS–SLE), patients with rheumatoid arthritis (RA), and healthy controls (HC). Fifteen non-CNS–SLE patients, 15 RA patients and 15 HC participants similar in age, education, and gender (female) were compared on tests of cognition, depression, and plasma levels of interleukin-6 (IL-6), dehydroepiandrosterone (DHEA), dehydroepiandrosterone sulfate (DHEA-S) and cortisol. Non-CNS–SLE patients demonstrated lower learning and poorer attention. Furthermore, non-CNS–SLE and RA patients had significantly lower levels of DHEA and DHEA-S than HC participants. Hierarchical regression analysis demonstrates that DHEA-S and IL-6 accounts for a unique portion of the variance in subject performance on measures of learning and attention after controlling for depression and corticosteroid treatment. This data highlights the value of hierarchical analyses with covariates, and provides evidence in humans of a relationship between peripheral cytokine levels and cognitive function. (*JINS*, 2001, *7*, 745–754.)

Keywords: Lupus, Neuropsychological, IL-6, DHEA-S, Cortisol

INTRODUCTION

Neuropsychological deficits can occur in systemic lupus erythematosus (SLE) patients without prior neurologic or psychiatric histories (Carbotte et al., 1986; Denburg et al., 1987; Hanly et al., 1993; Hay et al., 1992; Kozora et al., 1996; Rummelt et al., 1991a, 1991b; Wekking et al., 1991a, 1991b). In a recent study, 29% of the SLE patients without prior neurologic or psychiatric histories (non-CNS-SLE patients) and 31% of the rheumatoid arthritis (RA) patients demonstrated cognitive deficits in two out of eight cognitive domains (Kozora et al., 1996). The SLE patients were significantly different and below average in learning (of unstructured and structured verbal material and visual material) compared to the RA and healthy control groups HC (Kozora et al., 1996). This study also indicated that both SLE and RA patients were impaired compared to controls in attention (e.g., rapid auditory information processing, sustained visual tasks) and fluency skills (e.g., word generation to letter cues, visual design generation).

Mechanisms underlying those deficits remain unclear. Behavioral factors such as pain and fatigue could be associated with attentional impairment in these populations, although in other populations (i.e., chronic fatigue syndrome and fibromyalgia) these specific parameters have not fully accounted for decline in cognition (Tiersky et al., 1997). Similarly, the role of depression in the cognitive deficits of these patients has only recently begun to be addressed, and some have suggested that depressive symptoms do not account for the changes in cognitive functioning seen with these patients (Glanz et al., 1997). Disease duration, disease severity, global psychological distress and cor-

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ticosteroid use have not been identified as the major factors associated with cognitive impairment in SLE patients in prior studies (Denburg et al., 1987; Ginsburg et al., 1992; Hanly et al., 1994a, 1994b; Wekking et al., 1991) while others have supported a relationship between psychological distress, corticosteroid use and cognitive dysfunction (Hay et al., 1992, 1994; Kozora et al., 1996).

Unlike behavioral and nonspecific disease status indicators, analyses of biological correlates of autoimmune disease processes have been more fruitful in the search for the mechanisms of neuropsychological deficits. In SLE patients with more overt neurological or psychiatric symptoms, associations have been found between cognitive impairment and antineuronal antibodies and lymphocytotoxic antibodies (Denburg et al., 1987; Long et al., 1990). There is currently evidence suggesting that diffuse CNS presentations in SLE are associated with autoantibody activity, whereas more focal CNS presentations (i.e., strokes) are more related to vascular pathology (West et al., 1995). Unfortunately, immunological measures studied to date (including antiribosomal P, anticardiolipin and antineuronal antibodies) have not been consistently associated with cognitive deficits in CNS-SLE or non-CNS–SLE patients (Hanly et al., 1993; Kozora et al., 1996).

Other immunological factors active in both RA and SLE disease processes are also worth investigating. Similar to SLE patients, RA patients demonstrate evidence of systemic inflammation and cytokine release (al-Janadi et al., 1993). The inflammatory response such as that seen in both SLE and RA activates a variety of immune cells (macrophages and neutrophils) that contribute to tissue damage. This inflammatory process triggers a general or systemic response. The systemic reaction is mediated by the action of proinflammatory cytokines on distant target cells and is characterized by leukocytosis, an increased sedimentation rate, activation of complement and clotting cascades, synthesis and release of acute-phase proteins (including c-reactive protein). Interleukin-6 (IL-6) is one of many cytokines produced locally by macrophages, and it is a critical trigger of this acute phase response (Bauman & Gauldie, 1994).

In addition to regulating and coordinating responses between different types of immune cells, cytokines can also affect distant organs including the central nervous system (CNS). There has been growing evidence that nerve, endocrine and immune cells share common communication molecules and receptors, and that they are functionally linked to form a brain–endocrine–immune axis that integrates the physiological responses in the organism (DeSouza, 1993; Maier et al., 1998). Cytokines act directly within the CNS to alter growth and differentiation, to modulate neuronal and neuroendocrine activities, and to produce pyrogenic, somnogenic, thermogenic, anorexigenic, and behavioral effects (DeSouza, 1993). Proinflammatory cytokines are elevated in acute inflammatory responses and in both animal models and patient studies of RA and SLE (al-Janadi et al., 1993; Boswell et al., 1988; Elliott & Maini, 1995; Linker-Israeli et al., 1991; Maury & Teppo, 1989; Singh, 1992).

Hormonal functioning is also abnormal in SLE and RA patients and may provide another useful avenue for exploring mechanisms underlying cognitive impairment in these two autoimmune groups. Dehydroepiandrosterone (DHEA) is the most abundant adrenal steroid hormone in humans. DHEA is known to serve as an intermediate in sex hormone synthesis; however, the role of circulating DHEA is unclear. Serum levels of DHEA and its inactive form, DHEA-sulfate (DHEA-S), are lower in early life and rise to a maximum at about 25 years of age. DHEA levels tend to decline after that, reaching 15 to 20% of the maximum in individuals over the age of 70 (Orentreich et al., 1984). DHEA and several immunological parameters decline with aging, and it is believed that this decline in immune functioning is related to the decline in DHEA (Daynes & Areneo, 1992; Weksler, 1993). DHEA has also been reported to decrease in severe illness and chronic stress (Parker et al., 1986). Administration of DHEA to aged rodents also restores many immunological parameters (Weksler, 1993) and reverses stress effects (Ben-Nathan et al., 1992; Riley et al., 1990).

DHEA and DHEA-S have important interactions with the nervous system (Mellon, 1994; Roberts, 1990) and have been associated with cognitive functioning in both animal and human studies. Administration of DHEA and DHEA-S has had memory-enhancing effects in mice (Flood et al., 1988, 1992; Flood & Roberts, 1988; Melchior & Ritzmann, 1996). Lower DHEA and DHEA-S in humans with memory problems such as Alzheimer's disease and multi-infarct dementia have also been reported (Leblhuber et al., 1993; Nasman et al., 1991). Interestingly, it has been reported that patients with systemic lupus erythematosus also have lower levels of DHEA (Suzuki et al., 1995), a finding independent of steroid treatment. Treatment with DHEA in SLE improves clinical status (van Vollenhoven et al., 1994) although the impact on mental status has not been formally examined. In other patient groups, the administration of DHEA and DHEA-S has been mixed, with improvement noted in some but not in others (Wolf et al., 1997). In humans DHEA supplementation can improve both depression and memory function in middle-aged and elderly patients (Wolkowitz et al., 1997).

In addition to DHEA, assessment of the hormonal and neuroendocrine system can be accomplished by examining cortisol, a measure associated with the hypothalamic–pituitary–adrenal (HPA) axis. High levels of cortisol reflect stress and have been associated with negative pathophysiologic outcomes in humans (McEwen & Stellar, 1993). Evidence also suggests that increased HPA activity may impair cognitive functions (Carpenter & Gruen, 1982; Wolkowitz et al., 1990). In animal studies, hippocampal damage has been associated with chronic glucocorticoid administration (Sapolsky, 1993; Wolkowitz et al., 1990). Reduced hippocampal volumes in individuals with long-term posttraumatic stress disorder have also been reported (Bremner et al.,

1995; Gurvits et al., 1996), and several hypotheses regarding stress-induced hippocampal dysfunction and memory impairment have been proposed (McEwen, 1998). High cortisol levels may in fact be associated with cognitive dysfunction in autoimmune patients, although no studies exist at this time.

The goal of this study was to investigate possible biological mechanisms underlying cognitive dysfunction in non-CNS-SLE and RA patients. First we compared basal measures of inflammation (plasma IL-6) and hormone levels (cortisol, DHEA, DHEA-S) in non-CNS-SLE, RA, and HC participants. Secondly, we explored the relation of IL-6, DHEA, DHEA-S, and cortisol to standard scores of neuropsychological functioning in these individuals. In particular, we were interested in the affects of autoimmune processes on measures of attention, verbal fluency, and learning. Finally, since both glucocorticoids and the presence of depression have been shown to affect performance on neuropsychological tests in other populations (Hertel, 1998; Porterfield et al., 1997), we used hierarchical regression techniques to covary the effects of depression and corticosteroid use and to estimate the unique effect of cytokine and hormone production (IL-6, cortisol, DHEA, DHEA-S) on measures of attention, fluency, and learning. If these factors are important predictors of neuropsychological function, then these measures of inflammatory status and hormone production should result in significant partial correlations, indicating an effect beyond that of the covariates (glucocorticoid therapy levels and depressive symptoms).

MATERIALS AND METHODS

Research Participants

Participants for this study included 15 female SLE patients without neuropsychiatric symptoms (non-CNS–SLE) who participated in a larger neuropsychological study of neuropsychological, psychological and immunological functioning previously reported (Kozora et al., 1996). From the larger sample of 51 non-CNS–SLE patients, 15 had complete neuropsychological profiles as well as frozen sera samples available for analyses. These patients were then matched by age, education and gender (all females) to 15 RA and 15 healthy controls also from the larger comprehensive study. The RA group was originally recruited from local rheumatology clinics, and the HC group from local media announcements. Any individual (disease or healthy controls) with a history of learning disability, neurological illness (head injury, degenerative, vascular or metabolic disease, toxic exposure, seizures) or substance abuse were excluded. Persons with current or past major psychopathology such as Axis I disorders like depression, anxiety, or psychotic syndromes were also excluded. Determination of current or past Axis I disorders was based on structured interviewing using the SCID administered by a trained psychometrician (Spitzer et al., 1987). The SLE patients in this study are designated as non-CNS–SLE based on exclusion criteria which indicate no past or current history of neurological or psychiatric disease (including no history of learning disability, substance abuse, metabolic disorders, etc.).

Health Measurement

For the non-CNS–SLE and RA groups, length of diagnosis and prednisone dosage were obtained. The Systemic Lupus Erythematosus Disease Activity Index (SLEDAI) was administered to the SLE patients as a standard measure of disease activity (Bombardier et al., 1992). The SLEDAI consists of physician-rated disease manifestations (weighted scores) across multiple areas. For all participants, subjective overall health was measured on a 100-mm visual analog scale (VAS). This measured self-reported health (with 100 being *best overall health*) and disease activity (100 being *greatest symptoms*).

Neuropsychological and Psychological Measurement

A 4-hr battery of standard neuropsychological tests was administered, and raw scores from individual tests were transformed into demographically corrected *T* scores (see procedure in Kozora et al., 1996). Eight functional domain scores were developed by averaging *T* scores for tests within each individual domain. The eight cognitive domains are commonly accepted areas of neuropsychological function and include tests that are frequently (but not exclusively) associated with domains including Intelligence, Attention, Reasoning, Learning, Recall, Fluency, Language and Perceptual–Motor (Lezak, 1995). Please see Table 1 for a list of cognitive domains and associated tests. All of the neuropsychological tests in this battery have been standardized and validated in prior studies of normal and brain-damaged individuals (Lezak, 1995; Mitrushina et al., 1999; Spreen & Strauss, 1991). This approach (creating domain scores) was based on past studies showing that the reduction of neuropsychological data (typically derived by summing or averaging several scores) provided indices and scores relevant for the diagnosis of cerebral dysfunction (Adams & Heaton, 1985; Reitan & Davidson, 1974; Russell et al., 1970). The Beck Depression Inventory (BDI) was also administered as a measure of depressive symptomatology (Beck & Steer, 1987). Items were scored to reflect both cognitive and somatic features of depression. This test has demonstrated reliability and validity in a number of medical and psychiatric populations (Cavanaugh et al., 1983; Turner & Romano, 1984).

Inflammatory and Hormonal Measures

For all participants, blood samples were collected between 1100 and 1300 hr into heparinized tubes within

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Table 1. Cognitive domains and associated tests

Cognitive domain	Tests (reference)
Intelligence	Wechsler Adult Intelligence Scale–Revised (WAIS–R; Wechsler, 1981)
Attention	Digit Vigilance Test (Lewis & Kupke, 1977)
	Paced Auditory Serial Addition Test (Gronwall, 1977)
Reasoning	Category Test (Reitan & Wolfson, 1985)
	Trail Making Test (Reitan & Wolfson, 1985)
	WAIS–R Similarities (Wechsler, 1981)
Learning	Learning Component–Story Memory Test (Heaton et al., 1991)
	Learning Component–Figure Memory Test (Heaton et al., 1991)
	California Verbal Learning Test (Delis et al., 1987)
Recall	Delayed Component–Story Memory Test (Heaton et al., 1991)
	Delayed Component–Figure Memory Test (Heaton et al., 1991)
Fluency	Controlled Oral Word Association Test (Borkowski et al., 1967)
	Ruff Figural Fluency Test (Ruff et al., 1988)
Language	Complex Material subtest–BDAE (Goodglass & Kaplan, 1983)
	Reading Comprehension subtest–PIAT (Dunn, 1970)
	WAIS–R Vocabulary (Wechsler, 1981)
Perceptual–motor	WAIS–R Object Assembly (Wechsler, 1981)
	WAIS–R Block Design (Wechsler, 1981)

1 week of neuropsychological testing. Samples were centrifuged at 900g at 25°C for 10 min, and plasma was removed and stored at −70°C until assayed. Plasma IL-6 samples were transported in a frozen state to R & D Systems in Minneapolis, Minnesota, where Interleukin-6 levels were determined using an ELISA according to manufacturers instructions. All hormones (cortisol, DHEA and DHEA-S) were assessed by commercial radioimmunoassay (Diagnostic Products Company) according to manufacturer directions. Samples were reported for each participant. Intra- and interassay coefficients of variation for these hormones are less than 7% in our laboratory.

Data Analysis

Comparisons across the three groups were conducted using analysis of variance (ANOVA) and analysis of covariance (ANCOVA) controlling for total depressive scores on the BDI. Analysis of potential biological mediators of cognitive function consisted of hierarchical regression in which the covariates (BDI somatic and cognitive symptom subscales and a bivariate variable representing the use of prednisone) were entered as the first block. The potential mediators, DHEA, DHEA-S, cortisol and IL-6, were entered second as a block, and change in R^2, total model R^2, and partial correlation coefficients were examined for significance. In all cases an alpha level of .05 was used to indicate statistical significance. For completeness the same variables were entered as one block in a stepwise regression with an alpha level of .05 set as the entry level and an alpha level of .10 as the exclusion level. All analyses were performed with SPSS 8.0 for Windows (1988).

RESULTS

Comparisons Across Groups

Participant demographics can be found in Table 2. There were no differences across groups with regard to age or education. Health characteristics are also found in Table 2. Eight of the SLE patients, 2 of the RA patients and none of the healthy controls were on corticosteroid medication. The neuropsychological domain scores can be found in Table 3. As indicated previously, the scores in this table are *T* scores with a mean of 50 and a standard deviation of 10.

Results indicate significant group differences in learning [$F(2,42) = 5.28$, $p < .01$] and attention [$F(2,42) = 3.33$, $p < .05$] and nonsignificant trend differences in fluency [$F(2,42) = 2.82$, $p = .074$]. *Post-hoc* analyses indicate that the SLE and RA groups performed lower than controls on domains of attention. These results are similar to findings in the larger study (Kozora et al., 1998).

The Beck Depression Inventory (BDI) total score was significantly different across groups [$F(2,40) = 18.40$, $p < .001$]. The same was true for both the cognitive and somatic symptom subscales of the Beck Depression Inventory [$F(2,38) = 7.12$, $p < .01$; and $F(2,38) = 24.78$, $p < .001$]. As shown in Table 2, the SLE group had the highest total score (13.4) compared to RA (4.4) and controls (3.3). The same pattern was true for both the cognitive and somatic scales, with *post-hoc* testing confirming that the SLE group was significantly higher than either the RA or HC groups. In none of the BDI analyses were the RA patients significantly different from the HC group. Due to differences across groups on the BDI, group comparison on neuropsychological domains were additionally analyzed with BDI total score

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Table 2. Demographics and health characteristics for non-CNS–SLE, rheumatoid arthritis and healthy controls

	Lupus		Arthritis		Healthy controls	
Variable	*M*	*SD*	*M*	*SD*	*M*	*SD*
Demographics						
Age (years)	39.7	7.6	38.7	8.8	37.7	6.0
Education (years)	13.5	2.1	13.2	2.2	13.5	1.8
Health characteristics						
SLEADI	5.5	5.4	NA		NA	
Disease duration (mo.)	95.6	82.5	100.7	110.6	NA	
Subjective Health (VAS)	46.9	25.1	62.1	29.3	63.8	23.0
BDI Total Score	13.4	6.8	4.4	3.1	3.3***	3.2
BDI Cognitive Subscale	6.2	4.9	2.1	2.1	2.2**	2.0
BDI Somatic Subscale	7.2	3.2	2.4	1.7	1.4***	1.6

Note. Abbreviations: SLEADI, Systemic Lupus Erythematosus Disease Activity Index; BDI, Beck Depression Inventory; NA, not applicable in the health controls.
**$p < .01$. ***$p < .000$.

as a covariate. Results indicate that learning remains significantly different [$F(2,42) = 5.28$, $p = .01$] and attention has a trend significance for group difference [$F(2,37) = 3.0$, $p = .06$].

IL-6 and cortisol levels were not significantly different across groups (see Table 4). However, DHEA and DHEA-S levels were significantly different across groups [Fs$(2,42) =$ 11.25 and 6.09, respectively; ps $< .001$]. *Post-hoc* analysis indicate that DHEA-S levels in the non-CNS–SLE group are significantly lower ($p < .05$ by student Newman-Keuls) than the RA and healthy controls. Additionally, DHEA-S in the RA group is significantly lower than the HC group. Within the two patient groups only, there were no differences between patients taking steroid medication ($n = 10$) and patients not taking steroid medication ($n =$ 20) in DHEA, DHEA-S, cortisol, or IL-6 levels. Finally, dose levels of prednisone was not significantly correlated with any of the biological measures tested here (all rs $<$ $|.46|$, ps $> .10$).

Table 3. Neuropsychological domain scores by group

	Lupus		Arthritis		Healthy controls	
Score	*M*	*SD*	*M*	*SD*	*M*	*SD*
Intelligence	49.6	8.1	49.7	10.3	53.4	7.1
Attention	44.3*	5.5	44.9	5.5	48.9	4.9
Reasoning	51.5	6.5	47.6	8.3	52.0	6.6
Learning	41.2**	5.8	47.4	7.6	47.6	4.7
Recall	49.7	6.2	52.4	5.6	53.4	6.3
Fluency	46.1	6.3	47.1	6.7	52.0	8.3
Language	48.0	6.8	49.8	6.3	51.4	6.1
Perceptual	49.5	8.0	50.9	12.5	50.7	7.9

Note. n for each group is 15 for all domains except Intelligence where lupus group $n = 8$ and RA group $n = 14$.
*$p < .05$ (lupus differs from healthy controls).
**$p < .01$ (lupus group significantly different from arthritis and healthy controls).

Effects of Hormones and IL-6 on Neuropsychological Measures

In an effort to understand the role of the severity of depressive symptoms and the use of glucocorticoid therapy, and to understand further the relative impact of hormonal and cytokine levels on neuropsychological measures, a series of hierarchical regression models was performed. In these analyses, use of prednisone therapy and scores on the Beck Depression Inventory (BDI) were entered in the first step of the regression as covariates. The BDI was entered using both cognitive and somatic symptom subscales (Cavanaugh et al., 1983). Following this, hormonal and cytokine indices were entered to predict scores for the neuropsychological domain. Total model R^2 and partial correlations were reported. A significant partial correlation indicated that the biological index contributes uniquely to the variance in neuropsychological functioning, and suggests that the neuropsychological effects are not solely a result of either prednisone therapy or depressive symptoms.

Hormones and Neuropsychological Performance

As shown in Table 5, DHEA-S and IL-6 contributed a unique portion of variance beyond that of the covariates of prednisone therapy and depressive symptoms. Within the model predicting learning domain score, 46% of the variance was explained (total $R^2 = .46$, $p < .01$). Analysis of partial correlation coefficients shows that only the somatic depressive symptom subscale from the BDI and IL-6 contributed significantly to the variance in measures of learning. Neither cognitive symptoms of depression nor prednisone use were predictive of learning scores. As shown Table 5, the somatic symptoms of the Beck Depression Inventory that contributed significantly to the variance in learning scores, suggesting that increased somatic symptoms of depression resulted in decreased scores on measures of learning. These

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Table 4. IL-6, DHEA-S and cortisol by group

	Lupus		Arthritis		Healthy controls	
Assay result	*M*	*SD*	*M*	*SD*	*M*	*SD*
IL-6 pg/ml	2.7	1.4	9.8	4.3	4.9	8.7
DHEA-S μg/dl	36.7	39.9	96.7	69.2	147.4***	76.9
DHEA ng/ml	1.7	1.3	3.6	2.6	4.2**	2.0
Cortisol μg/dl	13.4	12.6	11.9	5.8	13.7	6.7

Note. All values obtained from serum.
**$p < .01$. ***$p < .000$.

self-reported somatic symptoms of depression accounted for 19% of the variance in learning scores ($pr = -.44$, $p < .01$). The relationship between only the somatic symptoms of depression and learning scores may be reflective of health, in that the self-reported overall health measure correlates negatively with somatic symptoms of depression on the Beck [$r(36) = -.52$, $p < .01$]. In other words, those with poor overall health tend to endorse many of the somatic symptoms of depression (i.e., poor sleep, low energy, weight loss). Additionally, higher levels of IL-6 in the plasma resulted in higher learning scores, and this relationship accounted uniquely for 17% of the variance in learning scores ($pr = .41$, $p < .05$). For completeness, a standard stepwise regression was run entering all of the same variables. As expected, only the BDI Somatic subscale and IL-6 levels entered as significant predictors of learning [$F(2,37) = 11.36$, $p < .000$]. Beta weights for each factor (full model) were $-.49$ for the BDI Somatic subscale ($p < .01$), which enters the equation first, and .38 for IL-6 ($p < .01$).

Within the model predicting the attention domain score, a total of 36% of the variance was explained (total $R^2 = .46$, $p < .01$). Here neither prednisone use nor either of the depressive symptom subscales were significant predictors of neuropsychological tests of attention. DHEA-S was marginally related to attention scores ($pr = .33$, $p = .06$). As would be expected from the literature, lower levels of DHEA-S in the plasma were related to lower scores on measures of attention. Also for completion, a standard stepwise regression was run predicting attention domain scores from the same predictors. The only factor to enter the equation was again DHEA-S [$F(1,38) = 16.36$, $p < .000$]. The Beta value for this factor was 0.55 ($p < .000$). Neither the full model R^2 nor any of the covariates or biological measures was significant predictor of neuropsychological measures of verbal fluency (total $R^2 = .16$, $p = .55$).

DISCUSSION

These results indicate that non-CNS–SLE and RA patients (with mild levels of disease activity) have lower levels of DHEA-S and DHEA compared to healthy controls. This is consistent with prior studies in SLE patients (Suzuki et al., 1995; van Vollenhoven et al., 1994) but further suggests that RA patients have alterations in DHEA metabolism. While there have been reported associations between prednisone dosage and lower DHEA, suggesting that corticosteroids can affect DHEA-S in autoimmune patients (Hedman et al., 1989), no such association was demonstrated in this small sample. There has also been prior work suggesting an interaction between DHEA and immune mediators such as

Table 5. Summary of hierarchical regression analysis of the effects of hormone and cytokine measures on learning and attention

	Learning			Attention		
Measure	*B*	*SE B*	β	*B*	*SE B*	β
Step 1						
Prednisone level	2.05	2.38	0.13	−0.70	2.21	−0.05
BDI Cognitive	0.24	0.31	.014	.028	0.28	0.19
BDI Somatic	−1.00	3.50	−0.54**	−0.42	0.33	−0.25
Step 2						
DHEA	0.60	0.58	0.20	−0.39	0.53	−0.15
DHEA-S	0.00	0.02	0.05	0.00	0.02	0.60**
Cortisol	0.00	0.16	−0.06	0.00	0.11	0.07
IL-6	0.21	0.09	0.34*	0.00	0.09	−0.01

Note. For the learning model Step 1 $R^2 = .25$; $_{\Delta}R^2 = .19$, $p < .05$. For the attention model Step 1 $R^2 = .13$; $_{\Delta}R^2 = .23$, $p < .05$.
*$p < .05$. **$p < .01$.

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interleukin-2 receptor and intercellular adhesion molecules in SLE (Straub et al., 1996). The relationship between DHEA and IL-2R and/or adhesion molecules in SLE patients have not to our knowledge, however, been examined as potential mediators of cognitive function. In this preliminary report we show that within cognitive domains, lower DHEA-S was marginally associated with low scores on attention. Given the statistically marginal nature of this finding, however, these data should be interpreted with caution viewed as a suggestion for further analysis only. While it is true that metabolites of DHEA may be critical in immune regulation, the ultimate mediator(s) of these cognitive differences is far from certain (Loria et al., 1996).

IL-6 contributed uniquely to measures of learning beyond the effects of depression, prednisone therapy, and all other hormonal measures. While it has been suggested that this relationship between IL-6 production and learning should be a negative one (Aubert et al., 1995; Gibertini et al., 1995; Pugh et al., 1998), recent reports using animal models of SLE have also showed a positive relationship between elevated immune parameters and learning (Hoffman et al., 1998). As noted by Hoffman et al. (1998), the important information to gain from these results is not whether or not there is a decrease or increase in scores, but rather that learning behavior is altered in this condition. Lesioning to both the fornix and hippocampal areas can result in increased measures of learning due to changes in stereotyped behavior and decreased distractibility (Hoffman et al., 1998). Furthermore, the present findings suggest that the relationship between IL-6 production and cognitive functioning may be quadratic (as in an inverted *U*-shaped function) whereby moderate levels facilitate but very low and very high levels disrupt learning capacity. Note that in this report there is a nonsignificant trend towards elevated levels of IL-6 in RA patients, but a near nondetectable level of IL-6 in the SLE patients. Others have reported that SLE patients in an active disease flare have elevated IL-6 levels (Linker-Israeli et al., 1991). At the same time, the SLE patients had significantly lower learning scores, but the RA patients with their higher level of IL-6 show learning capacities that are statistically identical to the healthy controls. Unfortunately, our data analysis involved an examination of within-group relationships, but clearly this is an avenue for further research; especially in SLE patients within an active disease flare.

Similarly, it must be noted that much of the experimental literature on cytokine activity and learning has evaluated animal models of induced cytokine activity whereby cytokines are induced or injected at *levels sufficient to cause at least some form of sickness behavior* including fever, malaise, and/or anorexia (Aubert et al., 1995; Gibertini et al., 1995; Pugh et al., 1998). In contrast, the present study recruited only those patients and controls who were in excellent current emotional health and *low* levels of disease activity. As such, cytokine levels in the patients were not significantly different from controls, but hierarchical regression analysis demonstrates that IL-6 levels *within the normal range* may be predictive of learning. This effect of IL-6 on learning is only evident once potentially confounding factors such as depressive symptoms and corticosteroid use are statistically controlled for. To date, the strongest evidence of IL-6 activity associated with central nervous system activity has been derived from cerebral spinal fluid studies (Hirohata & Miyamoto, 1990), but the current results suggest that peripheral levels of IL-6 are also informative in the study of cytokine production and neuropsychological functioning. A continued analysis of cytokine activity in association with inflammation may require investigations of both compartments (CSF *vs.* peripheral).

Finally, none of the biological indices studied here were related to measures of fluency. While the trend for lower fluency scores in the SLE and RA patients is consistent with earlier reports (Kozora et al., 1996), the relatively smaller sample size may account for the lack of statistical significance.

Additional studies should include closer analysis of relationships between hormones and cytokine activity. Cortisol enhances Type 2 cytokine (IL-4, IL-5, IL-6, IL-10, IL-13) responses leading to an enhanced antibody response whereas DHEA promotes a Type 1 cytokine (IFN-γ, TNF-β, IL-2, IL-3, IL-12) response which activates cell-mediated responses (Daynes et al., 1995). In autoimmune disease, a predominant Type 2 response would lead to greater production of auto-antibodies (Del Prete, 1998). However, this relationship is not simple as the two systems are not independent of each other. Both the immune and central nervous systems express and respond to a wide variety of cytokine, steroids, and other peptides which form the basis of bidirectional communication between these systems (Maier et al., 1998; Wilder, 1995). For example, a rise in proinflammatory cytokines like IL-2 can stimulate the release of ACTH leading to an increase in plasma cortisol (Maier et al., 1998). In the present study we noted reduced plasma levels of DHEA without significant changes in plasma cortisol. According to the above model, reduced DHEA in the face of unchanging cortisol has the potential to lead to increased auto-antibody production and higher levels of IL-6. Elevated cortisol without an increase in DHEA has the potential mechanism and could account for how stress exacerbates disease in SLE. In the present population, there was no indication of active inflammatory illness as measured by plasma IL-6 levels. Not surprisingly, there was no relationship between plasma cortisol and IL-6.

In conclusion, the present results support that adrenal androgen production is dysregulated in both SLE and RA. This dysregulation of androgen production, namely DHEA-S, was marginally related to measures of attention and concentration. Furthermore, although not reflective of group differences based on patient diagnosis, circulating levels of IL-6 were uniquely predictive of learning scores, and this effect was above and beyond that of the effect of somatic symptoms of depression. These data supplement the current growing literature on the relationship between cytokine production

and cognitive performance. We now demonstrate that, similar to animal models of autoimmune processes (Hoffman et al., 1998), immune activity measured here as circulating levels of IL-6 can predict scores on tests of learning in a positive direction. As indicated in the results, the disease activity in both the non-CNS-SLE and the RA patients was quite mild. In addition, the relatively small sample size of this study warrants caution and reinforces the need for replication in a larger sample. Furthermore, exploration of this relationship in both severe disease activity and relatively quiescent phases of autoimmune processes is needed to understand fully the function of this relationship.

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