Neuropsychological Impairments In Females with Primary Sjögren’s Syndrome: New Insights

The pSS literature has reported varying degrees of central nervous system involvement in individuals with this condition and secondary cognitive deficits associated with the disease.

By Tiffany Jennings, PsyD; Frederick Vivino, MD; Steven Mandel, MD; Kenneth Goldberg, PsyD; Edward Maitz, PhD; Bret Boyer, PhD

Primary Sjögren’s syndrome (pSS) is a progressive autoimmune disorder, affecting primarily the major exocrine glands. Prevalence rates vary from 0.2-4.8/100 adults depending on the diagnostic criteria employed.1-3 The pSS literature has reported varying degrees of central nervous system involvement in individuals with this condition and secondary cognitive deficits associated with the disease.4-12 The research has suggested such diverse outcomes as a complete sparing of functioning to dementia. Some of the difficulty interpreting the data is due to small sample size and lack of uniform diagnostic criteria used between and within studies.

Neuropsychological Functioning in pSS. Several studies have shown that verbal abilities (Verbal IQ) tend to be significantly less than non-verbal visuo/spatial abilities (Performance IQ) for individuals with pSS.7, 13, 21, 22 These studies suggest that this pattern of performance exists within the context of normal Full Scale IQ scores. In addition to these relative deficits in verbal functioning, verbal memory problems have also been reported within the context of relatively spared visual memory skills.15-19,20,21 However, not all studies have demonstrated memory deficits on objective testing, even in pSS patients who subjectively report memory problems.7,11,13,14,22-25 Although less prevalent in the literature, speech and language deficits and case reports of aphasia also have been reported.8,18-20 Many of the cognitive deficits that have been reported (verbal processing, verbal memory, language skills) imply left hemisphere dysfunction. However, some studies have found other cognitive deficits (attention and concentration7,11,20-23 and executive functioning11,20) that do not localize to the left hemisphere.

Neuroimaging findings have also been consistent with data from neuropsychological studies that have demonstrated neuropsychological impairment with evidence of periventricular, subcortical white matter, prefrontal, frontal, parietal, occipital and temporal lobe changes in individuals with pSS.3,9-15 Several studies have attempted to correlate neuropsychological test results with neuroimaging findings. One study found a significant association between ventricular volume and attention, psychomotor processing speed, and fatigue.16 Another found that reduced executive functioning correlated with lowered frontal cortex functioning.17

Research has also shown an association between pSS and the presence of psychiatric disturbances.13,19,26,27 Concomitant psychological disorders are felt to be important in the understanding and treatment of individuals with this condition. A variety of psychiatric disorders have been reported in pSS patients, including atypical mood disorders, psy-
chosis, paranoia, somatization, and histrionic personality disorder. In addition, women report more symptoms of fatigue, chronic pain, and sleep disturbances than do men.

Based on the extant literature, the following hypotheses were generated in an attempt to better define cognitive functioning in individuals with pSS using the American-European criteria. Because depression and age were felt to be variables that could potentially impact neuropsychological functioning, they were controlled for statistically.

1. Attention and executive functioning is expected to be poorer in pSS as compared to matched controls.
2. Intellectual functioning will be similar in the two groups. However, within the pSS group, the Verbal IQ score will be lower than the PIQ score.
3. Verbal memory will be lower in the pSS group as compared to matched controls.
4. Visual memory will be similar in the pSS group when compared to matched controls.

To test these hypotheses, neuropsychological testing was performed on 18 individuals with pSS and compared to test results from 17 controls matched for gender, race, and education. The patient sample all met the revised American-European criteria for the diagnosis of pSS. To our knowledge, this is the first study to describe neuropsychological functioning in this group using the revised American-European criteria.

Eighteen subjects were recruited from multiple sites, including the PENN Sjogren’s Syndrome Center (Dr. Frederick Vivino, Medical Director) at Presbyterian Hospital and Widener University. As the majority of individuals affected with pSS are women, all of the subjects recruited for this research project were female. Eligible subjects were between the ages of 18-70, and had a previous diagnosis of pSS. Students and staff from a local university (Widener University, Chester, PA) as well as members of the community, served as a comparison group.

Multiple neuropsychological measures were administered in order to examine the above hypotheses. All of the measures chosen frequently are used in clinical settings to evaluate cognitive functioning. The Trail Making Test (TMT) was used as a measure of concentration and processing speed while the Wisconsin Card Sorting Test (WCST) was used as a measure of executive functioning. Intellectual functioning was measured with the Wechsler Abbreviated Scale of Intelligence (WASI). Verbal memory was evaluated with the California Verbal Learning Test-II (CVLT-II) while visual memory was examined by the Visual Reproduction Subtest of the Wechsler Memory Scale-III (WMS-III).

The Depression scale from the Symptom Checklist 90-R (SCLR-90) was used as a measure of depression.

Data Analysis

Multivariate Analysis of Covariance (MANCOVA) was applied separately to test for differences in 1) IQ, using VIQ, PIQ, and FSIQ as dependent variables; 2) concentration and processing speed, using Trail Making Test A and Trail Making Test B times as dependent variables; 3) verbal learning, using CVLT-II total learning over trials 1 through 5, CVLT-II long delay free recall, and CVLT-II long delay cued recall as dependent variables; 4) visual memory, using WMS-III Visual Reproduction I, Visual Reproduction II, and Recognition subtest scores as dependent variables; and 5) executive functions, using WCST total errors and WCST total categories completed as dependent variables. Age and depression scores were subjected to simple correlations (Pearson R) with dependent variables (i.e., IQ scores, Trail Making Test A & Trail Making Test B scores, CVLT-II scores, WMS scores, and WCST scores) to ascertain whether age or depression constituted a significant covariate. Since depression score and age correlated significantly with Trail Making Test A and Trail Making Test B scores (age and Trail Making Test A score, R=.57, p<.001; Depression score and Trail Making Test B score, R=.34, p<.047), age and depression score were applied as covariates for the MANCOVAs testing group differences between pSS and comparison groups for tests of significant differences in performance on Trail Making Test A and Trail Making Test B. Since the MANOVAs and MANCOVAs included only two groups, and since the direction of the relationship was predicted by the hypotheses, one-tailed tests were applied for the comparison tests.
Participants were tested in one day by the primary researcher using the standardized procedures included in the test manuals. A demographic information form was also completed by each of the participants (Table 1). Each participant was tested for approximately 2.5 hours.

Raw scores for each of the measures were converted to standard scores and compared to performance scores for the normative groups on each measure (Table 2). Results were analyzed via the SPSS statistical program.

Results

Intelligence Quotient Scores. Overall IQ scores were significantly lower for the pSS group relative to the comparison group \(F(3) = 4.28, p = .012\). Performance IQ and Full Scale IQ did not differ significantly between groups, however the Verbal IQ was significantly lower for the Sjogrens group than for the comparison group \(F(1) = 11.82, p = .001\).

Concentration and Processing Speed. Trail Making Test A and Trail Making Test B times differed by age \(F(2) = 5.0, p = .006\) as a covariate, and differed significantly based on depression scores \(F(1) = 2.6, p = .04\). Trail Making Test A and Trail Making Test B scores did not differ significantly between pSS and comparison groups. Upon investigation of individual dependent variables, only Trail Making Test A time differed significantly based on age \(F(1) = 10.2, p = .001\).

Verbal Memory. CVLT-II scores were significantly lower for the pSS group than for the comparison group \(F(3) = 3.2, p = .02\). Examination of specific dependent variables revealed that total learning over trials 1 through 5 on the CVLT-II was lower for the pSS group than for the comparison group \(F(1) = 6.6, p = .008\), and the CVLT-II long-term delay cued recall significantly differed between the pSS and the comparison groups \(F(1) = 6.3, p = .009\).

Visual Memory. WMS-III Visual Reproduction I, Visual Reproduction II, and Recognition scores did not differ significantly based on age or depression scores as covariates, nor did they differ significantly between the pSS group and the comparison group. Upon closer inspection of individual dependent variables, however, WMS-III Visual Reproduction 1 was poorer for those with pSS than for those in the comparison group \(F(1) = 3.6, p = .03\).

Executive Function. WCST total number of errors and WCST number of categories completed did not differ significantly between the pSS group and the comparison group.

Discussion and Implications

The results of the current study support the hypotheses that Verbal IQ and verbal memory are reduced in the pSS group when compared to normal controls. Additionally, the pSS group in our sample demonstrated lower immediate visual recall on the Visual Reproduction I, subtest, which was not expected. There were no between group differences on the other neuropsychological functions measured including: concentration and processing speed, visual retention and recognition, and executive functions. The current study statistically controlled for age as the pSS group in our sample was older than the comparison group, and age has certainly been shown to impact neuropsychological test performance. Similarly, level of depression (higher in the pSS group) was also controlled for statistically because of the potential impact of this variable on test performance.

The results of the current study are consistent with many of the findings previously reported with individuals with pSS, even using older diagnostic criteria. Several studies have found reduced Verbal IQ
In addition, verbal memory has also been reported to be relatively impaired when compared to visual memory. These findings again support the possibility of selective left hemisphere involvement in the pSS population that shows neurological signs.

Several findings were not consistent with the previous literature, including the fact that the pSS group from the current study demonstrated reduced scores on a test of immediate visual recall and did not differ on measures of concentration and processing speed, or executive functioning. These findings may reflect the diagnostic criteria used, selection bias or may be truly part of the pSS symptom profile. Also, these findings may also be influenced by the fact that we controlled for age and level of depression, both of which have an impact on concentration and processing speed. Replication of these findings in a larger study using the American-European criteria will need to be performed to further examine this question.

Clinically, the current findings are important for physicians and individuals with pSS to understand. Formal neuropsychological testing can verify patient concerns regarding subtle changes in verbal skills and verbal memory that occur as part of this condition. Recognition of individual skill changes can validate patient symptoms and help lower anxiety levels. It should also trigger the development of compensatory strategies for losses [use of visual cues, developing auxiliary memory aids, having supportive family members know how to provide information for best results].

In addition, some of these verbal changes may impact work situations and/or family tasks and dynamics. Therefore cognitive remediation therapy may be justified to help Sjogren’s syndrome patients with declining skills remain as functional and productive for as long as possible by learning to make greater use of skills that have remained intact.

**Table 2. Neuropsychological Test Results**

<table>
<thead>
<tr>
<th>Test</th>
<th>Control mean</th>
<th>pSS mean</th>
<th>Mean Sq</th>
<th>F</th>
<th>Sig</th>
</tr>
</thead>
<tbody>
<tr>
<td>WASI VIQ Index Score</td>
<td>98.765</td>
<td>89.611</td>
<td>732.549</td>
<td>11.819</td>
<td>.002</td>
</tr>
<tr>
<td>WASI PIQ Index Score</td>
<td>105.941</td>
<td>102.278</td>
<td>117.333</td>
<td>1.084</td>
<td>.305</td>
</tr>
<tr>
<td>WASI FSIQ Score</td>
<td>102.412</td>
<td>100.778</td>
<td>23.343</td>
<td>.063</td>
<td>.803</td>
</tr>
<tr>
<td>Trails A</td>
<td>0.2353</td>
<td>0.278</td>
<td>0.016</td>
<td>0.049</td>
<td>.827</td>
</tr>
<tr>
<td>Trails B</td>
<td>0.294</td>
<td>0.778</td>
<td>2.045</td>
<td>2.533</td>
<td>.121</td>
</tr>
<tr>
<td>CVLT-II trial 1-5 Total words recalled</td>
<td>58.706</td>
<td>48.556</td>
<td>900.769</td>
<td>6.585</td>
<td>.015</td>
</tr>
<tr>
<td>CVLT-II LD free recall z score</td>
<td>0.147</td>
<td>-0.472</td>
<td>3.353</td>
<td>2.537</td>
<td>.121</td>
</tr>
<tr>
<td>CVLT-II LD cued recall z score</td>
<td>0.353</td>
<td>-0.639</td>
<td>8.601</td>
<td>6.267</td>
<td>.017</td>
</tr>
<tr>
<td>WMS-III VRI</td>
<td>11.470</td>
<td>9.167</td>
<td>46.408</td>
<td>3.572</td>
<td>.068</td>
</tr>
<tr>
<td>WMS-III VRII</td>
<td>8.706</td>
<td>9.6111</td>
<td>7.164</td>
<td>0.639</td>
<td>.430</td>
</tr>
<tr>
<td>WMS-III RECOG</td>
<td>11.529</td>
<td>10.500</td>
<td>9.265</td>
<td>1.081</td>
<td>.306</td>
</tr>
<tr>
<td>WCST Total # errors</td>
<td>79.059</td>
<td>69.556</td>
<td>789.586</td>
<td>1.008</td>
<td>.323</td>
</tr>
<tr>
<td>WCST # of categories completed</td>
<td>5.588</td>
<td>5.500</td>
<td>0.068</td>
<td>0.055</td>
<td>.816</td>
</tr>
<tr>
<td>SCL 90R – DEP Scale T score</td>
<td>47.353</td>
<td>61.77</td>
<td>1074.925</td>
<td>14.59</td>
<td>.001</td>
</tr>
</tbody>
</table>
The current study, although the first to our knowledge using the American-European criteria, is limited by the small sample size. Replication studies using a larger sample size would be useful. In addition, research correlating neuropsychological findings with neuroimaging studies would be useful. Finally, exploring the impact of depression on each individual variable and the quality of depression experienced by individuals with pSS would be helpful in future studies.

This study was reviewed and approved by the IRBs of Widener University and the University of Pennsylvania. Female participants were recruited from two sources (Widener University, PENN Sjogren’s Syndrome Center), with equivalent processes of recruitment/informed consent approved by both Widener University and the University of Pennsylvania.