The Developmental Social–Emotional Processing Disorder Is Associated with Right Hemisphere Abnormalities

Dara Sue Manoach, Ph.D., Thomas A. Sandson, M.D., and Sandra Weintraub, Ph.D.

Behavioral Neurology Unit, Beth Israel Hospital, and Harvard Medical School, Boston, Massachusetts, U.S.A.

Summary: We report the findings of neurological examination, neurophysiological studies, and neuroimaging studies in two samples of patients with the social–emotional processing disorder (SEPD). The first sample was selected anecdotally, on the basis of having the clinical presentation and neuropsychological features of SEPD, as well as documented neurophysiological abnormalities. The second sample was selected by serial chart review, blind to neurodiagnostic findings, on the basis of neuropsychological profile and clinical presentation. SEPD is a developmental syndrome characterized by a history of markedly poor interpersonal adaptation and relative deficiencies in nonverbal cognitive ability and paralinguistic communication skills. The neurodiagnostic findings support the hypothesis that SEPD is associated with early brain injury that affects the right hemisphere and results in its failure to support the adequate development of the cognitive, affective, and behavioral functions it normally subserves. Key Words: SEPD—Right hemisphere. NNBN 8:99–105, 1995

Dyslexia is a developmental disability affecting the language system that has been associated with neurophysiological dysfunction and both gross and cytoarchitectonic brain abnormalities disproportionately affecting the left cerebral hemisphere (1). Over the past 15 years, a learning disability, thought to arise from congenitally or early acquired damage affecting the right hemisphere, has been identified and described. This developmental syndrome, which we will refer to as the social–emotional processing disorder (SEPD), is characterized by (a) a history of deficient interpersonal relations, usually reflected in extreme shyness; (b) difficulties interpreting and producing paralinguistic (nonverbal) aspects of communication, including prosody, facial expression, and gesture; and (c) impaired visuospatial relative to verbal abilities (2–7). Associated features include attention deficits (6, 8); poor emotional adjustment and psychiatric disorders, particularly depression (9, 10); and soft neurological signs on the left side of the body (2, 7). Deficiencies in early academic achievement, if present, are typically in arithmetic and not in reading (5, 7, 11).

The SEPD has been associated with putative right-hemisphere dysfunction on the basis of neuropsychological profile and neurological examination findings (2, 3, 7, 12). However, relatively few studies have documented associated deviations in brain morphology or physiology (6, 9, 11). We present the findings of neurological examination, neurophysiological studies, and neuroimaging studies in two samples of patients with SEPD. The first study documents an association of the clinical syndrome of SEPD with right-hemisphere neurophysiological dysfunction in a sample of seven patients who were selected anecdotally, on the basis of having abnormal findings on neurodiagnostic tests. These patients are typical of patients in both samples and are described in detail. The second study employed systematic sampling methods and selection criteria to identify patients with the clinical presentation and neuropsychological profile of.


TABLE 1. Patient descriptions (Study I): demographics, history, behavioral observations, IQ scores, and achievement test percentiles

<table>
<thead>
<tr>
<th>Patient/</th>
<th>Social history/behavioral observations/emotional difficulty</th>
<th>Eye contact</th>
<th>Prosody/ affect</th>
<th>VIQ</th>
<th>PIQ</th>
<th>Read %ile</th>
<th>Spell %ile</th>
<th>Math %ile</th>
</tr>
</thead>
<tbody>
<tr>
<td>gender/</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>age/hand</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1/M/16/R</td>
<td>Chronically shy, few friends/no elaborated conversation/increasing withdrawal with onset of obsessive-compulsive symptoms and tics</td>
<td>Poor</td>
<td>Monotone/ flat</td>
<td>116</td>
<td>78</td>
<td>66</td>
<td>73</td>
<td>63</td>
</tr>
<tr>
<td>2/M/16/R</td>
<td>Chronically shy, “loner”, paucity of facial expression, discomfort, difficulty expressing feelings in words/depression</td>
<td>Poor</td>
<td>Monotone/ flat</td>
<td>119</td>
<td>92</td>
<td>88</td>
<td>34</td>
<td>16</td>
</tr>
<tr>
<td>3/M/15/R</td>
<td>Very shy, few friends/rarely initiates interaction/low self-esteem, sadness</td>
<td>Poor</td>
<td>Monotone/ flat</td>
<td>103</td>
<td>79</td>
<td>96</td>
<td>84</td>
<td>21</td>
</tr>
<tr>
<td>4/F/23/L</td>
<td>Actively avoids contact, social phobia, few friends/restricted facial expression and body gesture, no change in affect while discussing painful feelings/chronic depression</td>
<td>Normal</td>
<td>Normal/ constricted</td>
<td>100</td>
<td>101</td>
<td>82</td>
<td>77</td>
<td>30</td>
</tr>
<tr>
<td>5/F/14/R</td>
<td>Socially withdrawn, unmodulated voice, clumsy/stares at wall, hides face, language rapid-fire, stilted, odd inflection/inordinate time spent in fantasy</td>
<td>Poor</td>
<td>Monotone/ constricted</td>
<td>137</td>
<td>115</td>
<td>87</td>
<td>58</td>
<td>57</td>
</tr>
<tr>
<td>6/F/34/A</td>
<td>Shy/difficulty with self-expression, halting speech/low self-esteem, unprompted episodes of crying and sadness</td>
<td>Poor</td>
<td>Normal/ anxious</td>
<td>101</td>
<td>85</td>
<td>70</td>
<td>77</td>
<td>14</td>
</tr>
<tr>
<td>7/F/31/L*a</td>
<td>Introverted, aloof, interpersonal difficulties result in job loss/restricted gestures/severe depression</td>
<td>Poor</td>
<td>Monotone/ sad</td>
<td>108</td>
<td>80</td>
<td>82</td>
<td>77</td>
<td>30</td>
</tr>
</tbody>
</table>

VIQ, verbal IQ; PIQ, performance IQ.
*a Case with unilateral left-hemisphere electrophysiological findings.

SEPD and further explored the associated neurological, neurophysiological, and neuroanatomical abnormalities.

STUDY I

Patients and Methods

The seven patients who composed the first sample were evaluated at the Behavioral Neurology Unit of Beth Israel Hospital. They were selected on the basis of having (a) histories and neuropsychological findings that were consistent with the diagnosis of SEPD as determined by chart review according to the three criteria outlined above, and (b) neurodiagnostic studies that had disclosed abnormal features[e.g., EEG, computed tomography (CT), magnetic resonance imaging (MRI), brain electrical activity monitoring (BEAM)].

Summary of Patients

Table 1 presents patient descriptions that specify demographics, social history, behavioral observations, emotional features, and the findings of IQ and achievement tests. The sample was composed of three men and four women, ranging in age from 14 to 34 years, who had been referred for diagnostic evaluation of academic problems, interpersonal difficulties, or psychiatric disturbance. All patients had histories of severe interpersonal difficulties and poor emotional adjustment. On the basis of the examiners’ descriptions, which were noted in the charts, six of the seven patients had poor eye contact, five had abnormal spontaneous production of prosody, and all had affective abnormalities, including flatness, constriction, anxiety, and sadness.

Neurological History

On the basis of self-report, four of the seven patients were right-handed, two were left-handed, and one was ambidextrous. Four patients had histories suggestive of neurological injury before age 10, consisting of perinatal stress, hemipalsia influenza meningitis (age 3), hypoglycemic coma (age 7), and cerebral palsy (patients 3, 5, 6, and 7, respectively). Four patients had immediate family members with learning disabilities in arithmetic and spelling; psychiatric disorders consisting of depression and manic-depressive illness; similar interpersonal features (shyness); neurological symptoms consisting of left hemibody soft signs (patients 1, 2, 4, and 7); or more than one of these.

Neuropsychological Findings

As evaluations had been conducted for clinical purposes, patients were administered different tests, but

Neuropsychiatry, Neuropsychology, and Behavioral Neurology
major neurocognitive domains were assessed in each case. On the Wechsler Adult Intelligence Scale-Revised (WAIS-R) or Wechsler Intelligence Scale for Children-Revised (WISC-R), six of seven patients had a higher verbal than performance IQ, which did not result simply from the timed nature of the performance subtests. All patients showed deficient performance on one or more standard neuropsychological tests of attention, including measures of immediate span [Digit and Visual Span (13)], freedom from distractibility [Stroop Test (14)], set maintenance and alternation [Trail Making Test (15)], word-list generation (16), and response inhibition [Motor Go–No-Go paradigm (17)]. All patients showed impairments in visuospatial ability relative to language-based cognitive skills, which were in the average to above-average range. Several patients were deficient in complex perceptual judgments on Judgment of Line Orientation (18) and had deficient constructional ability on the basis of piecemeal, distorted copies of the Rey–Osterreith Complex Figure (19). One patient showed a significant reduction in delayed recall of nonverbal versus verbal materials on both the Wechsler Memory Scale, Revised (WMS–R) (13) (Logical Memory I & II: 81 and 73 percentile versus Visual Reproduction I & II: 74 and 32 percentile) and the Warrington Recognition Memory Test (20) (Words: 49 of 50 versus Faces: 30 of 50, difference significant at p < 0.05). Arithmetic subtest percentile scores were lower than those for Spelling and Reading on the Wide Range Achievement Test–Revised (WRAT–R) (21). Speech prosody was formally tested (procedure described elsewhere) (22) in five patients, all of whom displayed deficiencies in the discrimination, repetition, and/or spontaneous production of affective and/or nonaffective prosody.

Neurological Examination and Neurodiagnostic Tests

Neurological examinations showed disproportionate left-sided soft signs in five of seven patients. In six of seven patients, neurophysiological studies implicated disproportionate right-hemisphere dysfunction. Four patients showed a predominance of right-hemisphere EEG abnormalities: two with slowing and two with epileptiform activity (one emanating from central and to a lesser extent, parietal regions, and the other from the temporal lobe). Two patients showed right posterior abnormalities on BEAM auditory and visual evoked responses.

The neurological, CT, and EEG findings for patient 7 indicated left-hemisphere abnormalities. Her neurological examination showed a right hemihypoplasia and a mild right hemiparesis with increased deep tendon reflexes and an extensor plantar response. An EEG demonstrated left temporal epileptiform activity, and CT revealed that the left hemisphere was smaller than the right. This patient was left-handed and had been noted to drag her right foot at the onset of walking, at which time she was diagnosed with cerebral palsy. She showed a left-ear advantage on a variant of the dichotic listening test for digits (83.3% correct for digits presented to the left-ear versus 66.7% correct for digits presented to the right ear), suggestive of anomalous dominance for language (23). This patient is presented in greater detail elsewhere (24).

Summary

This sample of seven adolescent and adult patients with SEPD is similar in clinical features to one we described earlier (7). These patients had features associated with SEPD, including poor emotional adjustment and psychiatric illness, attention deficits, poor achievement in mathematics relative to basic linguistic abilities, and left-hemisbody soft neurological signs. In addition, all patients had either a personal history suggestive of early neurological injury or a family history of interpersonal difficulties, psychiatric disorder, learning disability, or neurological symptoms. Our report adds the documentation of associated right-hemisphere neurophysiological dysfunction in six of the seven patients. One patient, with apparent anomalous cerebral dominance, had left-hemisphere abnormalities on neurological examination, EEG, and CT. These findings prompted us to undertake a more systematic investigation of the neurological, neurophysiological, and neuroanatomical correlates of the clinical syndrome of SEPD.

STUDY II

Patients and Methods

Selection Procedure

We reviewed the medical records of a series of 441 patients between the ages of 14 and 65 years for possible inclusion in this study. All had been seen for neuro-psychological evaluations over a 1.5-year period at the Behavioral Neurology Unit of Beth Israel Hospital, Boston. Patients whose clinical work-up did not include a neurological examination or neurodiagnostic studies were excluded. Patients with a diagnosis of acquired brain disease or with a history of significant brain injury after the age of 10 were also excluded. Of those remaining, 17 patients, seven women and 10
TABLE 2. Demographic, historical, and neuropsychological findings in patients grouped by laterality of neurological examination and neurodiagnostic study findings (Study II)

<table>
<thead>
<tr>
<th>Patients</th>
<th>Right-hemisphere (n = 8) (%)</th>
<th>Left-hemisphere (n = 2) (%)</th>
<th>Bilateral (n = 6) (%)</th>
<th>Normal (n = 1) (%)</th>
<th>Total (n = 17) (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender, M</td>
<td>63</td>
<td>0</td>
<td>67</td>
<td>100</td>
<td>59</td>
</tr>
<tr>
<td>Hand, R</td>
<td>63</td>
<td>0</td>
<td>83</td>
<td>0</td>
<td>59</td>
</tr>
<tr>
<td>Abnormal neuro exam</td>
<td>75</td>
<td>100</td>
<td>33</td>
<td>0</td>
<td>59</td>
</tr>
<tr>
<td>Abnormal neurodiagnostic</td>
<td>50</td>
<td>100</td>
<td>100</td>
<td>0</td>
<td>71</td>
</tr>
<tr>
<td>Early brain injury</td>
<td>75</td>
<td>50</td>
<td>0</td>
<td>0</td>
<td>59</td>
</tr>
<tr>
<td>Family history</td>
<td>25</td>
<td>50</td>
<td>67</td>
<td>100</td>
<td>47</td>
</tr>
<tr>
<td>Psych history</td>
<td>63</td>
<td>50</td>
<td>83</td>
<td>100</td>
<td>71</td>
</tr>
<tr>
<td>Poor eye contact</td>
<td>63</td>
<td>100</td>
<td>67</td>
<td>100</td>
<td>71</td>
</tr>
<tr>
<td>Abnormal prosody</td>
<td>88</td>
<td>50</td>
<td>67</td>
<td>0</td>
<td>71</td>
</tr>
<tr>
<td>Attention deficits</td>
<td>88</td>
<td>100</td>
<td>100</td>
<td>100</td>
<td>94</td>
</tr>
<tr>
<td>Poor math ability</td>
<td>38</td>
<td>100</td>
<td>67</td>
<td>100</td>
<td>59</td>
</tr>
</tbody>
</table>

men, ranging in age from 14 to 65, met criteria for SEPD on the basis of neuropsychological profile and history. The criteria for diagnosing SEPD were as follows: (a) normal verbal intellectual ability (verbal IQ ≥90); (b) a relative deficit in nonverbal intellectual ability [performance IQ 10 or more points lower than verbal IQ. A 10-point IQ discrepancy is significant at the 0.05 level (25)]; (c) a lifelong history of markedly poor interpersonal adaptation; and (d) diminished eye contact, prosody or both on observation and, in some cases, on formal assessment of the prosodic aspects of speech [procedure described elsewhere, (22)].

Results

Summary of Neurological Examination and Neurodiagnostic Study Findings

Table 2 groups the sample according to the laterality of abnormalities as documented in the neurological examination, on neurodiagnostic studies or both. Of the 17 patients, eight had right-hemisphere abnormalities, two had left-hemisphere abnormalities, six had bilateral abnormalities, and one had normal findings.

Right hemisphere abnormalities (n = 8)

On neurological examination, six of the eight patients had signs and symptoms reflecting right cerebral involvement, which included asymmetrical deep tendon reflexes and left hemihypoplasia (n = 3) and “soft” signs consisting of asymmetrical posturing on complex gait (L > R), and decreased rapid alternating movements on the left (n = 3). On neurodiagnostic studies, four patients had right-hemisphere abnormalities: two had previously undetected temporal lobe epileptiform activity, one had a frontal lobe arteriovenous malformation, and one had nonspecific temporal and occipital abnormalities on BEAM auditory and visual evoked responses. Three patients had normal neurodiagnostic findings, and one patient had not undergone neurodiagnostic studies.

Left Hemisphere Abnormalities (n = 2)

Both patients had asymmetrical dystonic posturing (R > L) on complex gait and left temporal lobe epileptiform activity on EEG. One patient also had focal atrophy in the temporal lobe.

Bilateral Abnormalities (n = 6)

Two patients showed bilateral dystonic posturing of the arms on complex gait. All six patients had bilateral abnormalities on SPECT, EEG or both, and one also had bilateral medial temporal arachnoid cysts.

Normal Findings (n = 1)

One patient had normal findings on neurological examination, neuroimaging, and neurophysiological studies.

Historical and Neurological Characteristics

Cerebral Dominance

Determination of handedness was by self-report. Overall, 10 patients were right-handed, four were left-handed, and three were ambidextrous. Interestingly, neither patient with left-hemisphere abnormalities was right-handed, and in one of these patients, the findings of a presurgical intracarotid amobarbital pro-
procedure were consistent with right-hemisphere dominance for language.

Psychiatric History

Sixty-five percent (n = 11) of the patients had either previous or current depression. Sixty-five percent (n = 11) of the patients had other psychiatric illnesses including eating disorders, psychotic disorders, obsessive-compulsive disorder, and panic disorder. Only one patient, a 14-year-old, had no diagnosed psychiatric disorder.

Neurological Risk Factors

Fifty-nine percent of the patients had histories suggestive of early brain injury consisting of pre- or perinatal insult, significant head injury and/or a neurological illness (e.g., encephalitis) before age 10. Forty-seven percent of the patients had family histories of major psychiatric illnesses or developmental disorders including depression, alcoholism, obsessive-compulsive disorder, and learning disability, including dyslexia. In all, 15 of the 17 patients reported one or both of these factors in their histories.

Neuropsychological Characteristics

Fifty-nine percent of the patients reported either a history of mathematical learning difficulty and/or showed worse achievement in mathematics than in reading or spelling as measured by the WRAT-R. All but one of the patients were deficient on standard neuropsychological tests of attention (described in Study I), eight reported a history of attention deficits and three had previously been diagnosed with attention deficit disorder, two with hyperactivity.

DISCUSSION

The developmental syndrome of SEPD is characterized by deficiencies in functions normally subserved by the right hemisphere. The current studies document the presence of neurophysiological and neuroanatomical abnormalities in patients with SEPD. The majority of patients showed evidence of unilateral right-cerebral abnormalities. However, a substantial number had bilateral cerebral abnormalities and several had unilateral left-cerebral abnormalities. In addition, almost every patient had a personal history suggestive of early neurological injury or a family history of learning difficulties, interpersonal deficits, psychiatric disorder, or neurological symptoms.

Hypotheses regarding the bases of these associations are discussed below.

All of the three patients whose neurodiagnostic findings implicated the left hemisphere had anomalous cerebral dominance. All three were left-handed, and two had evidence of right-hemisphere dominance for language: one on the basis of an intracarotid amobarbital procedure and the other on the basis of dichotic listening performance. We have discussed this paradoxical association of SEPD with left hemisphere dysfunction in greater detail elsewhere (24). The explanation we prefer is that early left-hemisphere injury resulted in a displacement of language and handedness to the right hemisphere and that this reorganization interfered with the development of functions that the right hemisphere normally subserves. Dominance for language is subject to normal variations and can “relocate” to the right hemisphere in the case of early injury (26–28). In contrast, functions subserved by the right hemisphere (e.g., visuospatial skills and the spatial distribution of attention) are seldom localized in the left hemisphere even in patients with early right-hemisphere injury, anomalous dominance for language and/or nonright-handedness (28, 29). For this reason, functions subserved by the right hemisphere may be vulnerable to disruption by early injury to either or both cerebral hemispheres.

The histories of early diffuse encephalopathic events (e.g., meningitis, hypoglycemic coma) in some patients and the presence of bilateral cerebral abnormalities in a substantial number of patients also indicate that although the neurodevelopmental injury that gives rise to SEPD disproportionately affects right-hemisphere functions, it may not affect the right hemisphere exclusively. Diffuse bilateral brain insults might give rise to SEPD on the basis of the hypothesized vulnerability of right-hemisphere functions or on the basis of asymmetrical damage, although it is the left hemisphere that is thought to be at increased risk (30, 31). Bilateral abnormalities may also result from early unilateral injury. In animals, prenatal unilateral ablation leads to anatomical changes in both proximal and distal brain regions as well as in regions contralateral to the injury [e.g., (32)]. In humans, there is some evidence that early unilateral lesions can give rise to bilateral abnormalities of function. This has been demonstrated in individuals with comportmental learning disability and with infantile hemiplegia (33, 34). SEPD may be analogous to dyslexia, in which there are often bilateral neurodevelopmental abnormalities in brain anatomy and physiology (usually left more than right) but functions associated with one hemisphere (the left in dyslexia) are disproportionately affected (1). In our report, the range of
neurodiagnostic findings and the histories suggestive of both early-acquired and genetic etiological factors imply that the etiologies and brain abnormalities associated with the clinical syndrome of SEPD are heterogeneous.

The features of SEPD as defined here and in previous studies are a relative deficiency of nonverbal intellectual ability, poor paralinguistic communication skills, and a developmental history of markedly poor interpersonal adaptation. Our findings also support the association of SEPD with attention deficits, mathematical learning difficulties, depression, and other psychiatric disorders. None of these associated features was present in all patients. Prospective studies using larger samples and standardized measurements of symptoms, such as deficient attention and eye contact, might explore the relations between the associated features, their relationship to brain anatomy and physiology and to possible etiologies such as genetic factors and the timing of brain injury.

Consistent with previous reports, attentional deficits were present in the vast majority of patients (6, 8). Many of the patients met Wender's Utah criteria for attention deficit disorder [ADD, (35)], and several had been diagnosed with ADD in the past. Standard clinical neuropsychological measures of attention are multidimensional and do not adequately delineate the exact nature or specific anatomic basis of attentional disturbance. For this reason, it is not known whether the nature or degree of attentional disturbance differs in individuals with SEPD versus those with ADD alone. The presence of attention deficits in SEPD is not surprising, because in normal adults the right hemisphere provides the primary neuroanatomical substrate of a distributed large-scale neural network for spatial distribution of attention (36–38). A preliminary study of spatially directed attention as measured by eye movements found that individuals with SEPD have deficits that distinguish them from both normal and dyslexic subjects (39). This suggests that the use of objective physiologically based measurements of attention may aid in the delineation of individuals with developmental disorders that affect aspects of attentional functioning.

Individuals with SEPD also have difficulty with the modulation of affective experience. Our study further documents the comorbidity of SEPD with refractory depression and other neuropsychiatric disorders (9–11). Because of the overlapping phenomenology, individuals with SEPD may be diagnosed with schizoid personality, social phobia, and Asperger's syndrome (40), and consequently, may not be referred for further neurodiagnostic evaluation. Neurological workup of several of the patients presented here revealed previously undiagnosed epileptiform activity. Treatment with anticonvulsant medications resulted in seizure control and, in some cases, in a corresponding amelioration of neuropsychiatric symptoms (e.g., Study I, case 6: the initiation of phenobarbital was associated with a marked improvement in mood, increased eye contact, better prosody, and increased social interaction). The clinical manifestations of seizures were identified only retrospectively (e.g., episodes of "sudden dread," dissociation, and unprecipitated crying, sadness, and confusion). This suggests that patients with atypical or refractory psychiatric disorders and histories consistent with SEPD should undergo neurodiagnostic evaluations.

Several methodological features of our studies may limit the applicability of the findings. The sample was comprised of adolescents and adults with residua of a developmental learning disability. Individuals with SEPD who come to medical attention as infants and children may differ with regard to the specific manifestations of the syndrome. In addition, diagnosis depended, in part, on retrospective reports and clinical judgments. In the majority of cases, however, confirming information from past medical records was also available. Finally, the requirement of neurodiagnostic tests or neurological examinations may have biased the current selection to be a more neurologically impaired group.

Our findings provide evidence from neurological examinations, neuropsychological studies, and neuroimaging studies that the clinical syndrome of SEPD is associated with cerebral dysfunction. This is consistent with the hypothesis that SEPD arises from an early acquired or genetic brain dysfunction that affects the right cerebral hemisphere and results in its failure to support the adequate development of the cognitive, affective, and behavioral functions that it subserves in the normal adult. We hypothesize that right-hemisphere functions may be compromised on the basis of direct injury to regions that subserve them or on the basis of injuries elsewhere that result in a relocation of other functions (e.g., language) to the right hemisphere at the expense of functions it normally subserves. In this way, SEPD can be grouped with other developmental processing disorders such as dyslexia, which arises from brain abnormalities that disproportionately affect left-hemisphere functions (1) and comportmental learning disability, which is associated with early damage to the frontal lobes (33, 41).

REFERENCES

16. Spreen O, Benson AL. Neurosensory Center Comprehensive Examination for Aphasia. Victoria, BC: Neuropsychological Laboratory, Department of Psychology, University of Victoria, 1969.