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Deficient antisaccades in the social–emotional processing disorder

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We investigated whether adolescents and adults with the developmental social–emotional processing disorder (SEPD) exhibit deficits in visual attention, as measured by eye movements, when compared with dyslexic and normal control subjects. On the antisaccade task, subjects with SEPD made more errors than either control group and were the only group to show a decrease in performance accuracy compared with prosaccade. This deficit in inhibiting reflexive shifts of attention and gaze suggests that individuals with SEPD have dysfunction of the prefrontal component of the right hemisphere dominant network for spatially directed attention.

Key words: Developmental learning disability; Eye movements; Frontal eye field; Prefrontal cortex; Social–emotional processing disorder; Spatial attention

Introduction

Specific learning disabilities are a class of disorders that arise from neurodevelopmental abnormalities. The social–emotional processing disorder (SEPD), which has also been referred to as the non-verbal learning disability and the right-hemisphere learning disability, is a syndrome thought to arise from congenitally or early acquired damage to the right hemisphere.[1] It is characterized by a history of deficient interpersonal relations, usually reflected in extreme shyness; difficulties interpreting and producing paralinguistic (non-verbal) aspects of communication including prosody, facial expression and gesture; and impaired visuospatial relative to verbal abilities. Associated features include poor emotional adjustment and psychiatric disorder, particularly depression, and deficient academic achievement in arithmetic but not in basic linguistic abilities.[1,2]

SEPD has been associated with right hemisphere dysfunction on the basis of the neuropsychological profile and the findings of neurological examination, neurophysiological studies and neuroimaging studies.[1–4] In normal adults the right hemisphere provides the primary neuroanatomical substrate for the spatial distribution of attention.[5,6] This large-scale neurocognitive network has its principal anatomical components in the prefrontal and posterior parietal cortices and the cingulate gyrus regions which, in animals, regulate both shifts of attention and accompanying shifts of gaze.[7] The frontal eye field triggers saccades concerned with the intentional exploration of the visual environment, including correct antisaccades, while the parietal eye field triggers saccades made reflexively in response to the appearance of a visual target.[8]

Individuals with SEPD have attention deficits, but these deficits have not been well characterized.[1] The purpose of this study was to better delineate the nature and anatomical substrate of spatial attention deficits in SEPD by using validated experimental eye movement protocols that are linked to specific anatomical components of the right hemisphere network. Eye movement measurements serve as objective, physiologically based indices of visual attention. We hypothesized that individuals with SEPD would exhibit deficits in specific aspects of spatially directed attention on the basis of presumed right hemisphere dysfunction. In particular, we expected that they would have difficulty with complex intentional aspects of visual attention. We tested this with an antisaccade protocol which requires the inhibition of a reflexive saccade and the substitution of an intentional gaze in the direction opposite the appearance of a target. We did not expect SEPD subjects to show difficulty with prosaccade which involves a more reflexive gaze to a visual target or with the simple maintenance of fixation in the absence of distraction. We did not expect to see any deficits in visual attention on these tasks in either normal or dyslexic control groups.

Table 1. Demographics and selected neuropsychological evaluation findings for SEPD and dyslexic subjects

Subject	Age	Sex	VIQ	PIQ	R%	S%	A%	DSF	DSB	VSF	VSB	TC L	TC R
SEPD													
1	13	M	113	93	85	66	39	5	4	5	5	1	2
2	20	M	103	79	96	84	21	7	6	5	5	0	0
3	21	M	111	90	94	88	63	6	7	4	4	–	–
4	15	F	137	115	87	58	57	7	7	6	7	0	0
5	23	M	116	78	66	73	63	7	6	6	6	–	–
6	34	M	110	82	68	25	21	6	5	4	3	0	0
7	13	M	127	96	98	93	99	8	7	8	6	0	0
8	18	F	100	87	75	68	12	9	6	5	4	1	2
Dyslexia													
1	24	F	102	131	45	13	30	6	3	6	5	–	–
2	23	F	102	106	25	13	24	5	4	6	5	0	1
3	21	M	102	118	23	45	75	5	5	5	5	0	0
4	46	F	108	121	58	73	37	6	7	8	7	0	0
5	39	F	105	117	45	45	42	5	4	7	7	–	–

VIQ, verbal IQ; PIQ, performance IQ; percentiles for Wide Range Achievement Test – Revised – R%, single word reading; S%, spelling; A%, arithmetic; DSF, digit span forward; DSB, digit span backward; VSF, visual span forward; VSB, visual span backward; Random Shape Target Cancellation test with 30 targets in each hemispace: TC L, left omissions; TC R, right omissions.

Subjects and Methods

Subjects: All subjects gave informed consent and experimental protocols were approved by the Committee on Clinical Investigations. Eight SEPD and five subjects with dyslexia were selected from a clinical sample on the basis of history and neuropsychological findings (See Table 1). The history was compiled from medical records and clinical interview.

Subjects with SEPD met the following criteria: lifelong history of interpersonal difficulties, normal verbal intellectual function (Verbal IQ ≥ 90), superior verbal relative to non-verbal ability (verbal IQ ≥ 10 points higher than performance IQ), normal reading achievement on the Wide Range Achievement Test-Revised (WRAT-R), and impaired paralinguistic communication skills consisting of poor eye contact and/or impairments in prosody.

Subjects with dyslexia showed normal non-verbal intellectual function (performance IQ ≥ 90) and deficient reading achievement (WRAT-R reading score ≥ 30 percentile points below performance IQ).

Six normal subjects (four males, two females) were recruited from the hospital staff and their families. They were matched for age and sex with the SEPD group (age: normal controls 22.167 ± 10.01 years, subjects with SEPD 19.65 ± 6.87; $F = 0.266$, $p = 0.6133$) and had no history of neurological disorder, psychiatric disease, learning disability or academic difficulty. Subjects with SEPD were younger than the dyslexics (dyslexic group 30.60 ± 11.19; $F = 4.445$, $p = 0.0511$). Females were disproportionately represented in the dyslexic group.

Testing procedures: We only considered patients with SEPD and patients with dyslexia for entry into the study if they had undergone neuropsychological evaluation. As this evaluation had been conducted for clinical purposes, subjects were not administered a consistent battery of tests, but major cognitive domains were assessed in each case. These domains were general intellectual ability (WAIS-R or WISC-R); attention, including measures of immediate span (digit and visual span); freedom from distractibility (Stroop test[9]), set maintenance and alternation (trail making test[10]), word list generation[11] and response inhibition (motor go–no go paradigm[12]); memory, including the Wechsler Memory Scale – Revised;[13] language, including the WRAT-R[14] and paralinguistic communication on a formal test of speech prosody;[15] and visuospatial ability, including complex perceptual judgment on judgment of line orientation,[16] visuomotor scanning on a random shape target cancellation test[12] and constructions using the Rey–Osterreith complex figure.[17]

All subjects underwent a bedside neuro-ophthalmologic examination that evaluated visual fields to confrontation, smooth pursuit, saccades and partial field optokinetic nystagmus. Eye movement data were obtained during the three experimental protocols: fixation stability, prosaccade and antisaccade.

Eye movement recording method: Subjects were tested using an Applied Science Laboratories video-based pupil center to corneal reflection system (model 4000). The subjects' point of regard is determined by the measurement of the center of the pupil with respect to the center of the corneal reflection. The accuracy of the system is ±0.75° with a temporal resolution of 16 ms.

Experimental protocols: Fixation stability required the maintenance of focused attention and gaze on a cross in the center of a CRT screen. Subjects were instructed to look at the cross as steadily as they could for 1 min. Prosaccade tests the ability of subjects to make simple shifts of attention and gaze to visual targets appearing to the right and left of the screen center. Subjects fixated a 0.5 × 0.5° cross in the center of the screen. The cross disappeared and was immediately followed by an empty box that appeared 8° to either the right or left of the center for a duration of 200 ms. Subjects were told to look at the box as soon as it appeared, to wait for a second box containing an 'X' to appear in the same location and to maintain fixation until the second box disappeared. The second box appeared on the screen for 450 ms 700 ms after the erasure of the first box. After the erasure of the second box, subjects were instructed to refixate the central cross which had reappeared. Antisaccade increased attentional demands by requiring subjects to inhibit the more automatic tendency to look towards a new stimulus and to substitute an alternative behavior. The protocol was similar to that of prosaccade but there was no second box and the subjects were instructed to look at the side of the screen opposite to the location of the target.

Experimental protocols were preceded by a period of practice which lasted until eye movement behavior indicated that the subject understood the task. Experimental trials ran continuously for 2 min. Stimuli were evenly distributed to the right and left of the screen center and were presented in random order.

Data analysis: All raw eye position data were processed to yield a record of fixations and saccades. The dependent variable for fixation stability was the proportion of time spent maintaining gaze within the 2 × 2° area around the central cross during the 1 min test period. Dependent variables for prosaccade and antisaccade were percentage correct trials and mean saccade latency for targets that occurred in the right and left visual fields. Only correct trials were included in the analyses. For prosaccade a correct trial was defined as any trial in which the initial saccade was in the direction of the target and in which the space subtended by 2 × 2° of visual angle around the target position was fixated prior to target erasure. For antisaccade, a correct trial was any trial in which the initial saccade after the appearance of the target was in the direction opposite from the target.

One-way analyses of variance were used to compare groups on fixation stability and selected neuropsychological measures of attention. Repeated measures analyses of variance were used to compare groups on prosaccade and antisaccade variables for targets occurring in the right and left visual fields. *Post hoc* tests were planned comparisons. Paired *t*-tests were used for within-group comparisons. A statistic was considered to be significant if its exact two-tailed probability value was < 0.05.

Results

Eye movement studies: All subjects had normal oculomotor function. There were no significant differences between groups with regard to fixation stability, although normal individuals showed a trend to be less stable than dyslexics (See Table 2). There were no significant main effects for visual field of target presentation for either prosaccade or antisaccade variables, nor were there any significant interactions of visual field by diagnosis. Thus data from the right and left visual fields are combined in table 2. Subjects with SEPD showed a trend to worse performance than normal subjects on prosaccade (proportion correct) but were not different from

Table 2. Means (s.d.) and statistical analyses of the eye movement measures combined across visual field for the prosaccade and antisaccade variables

Comparisons	Fixation stability	Prosaccade % correct	mean latency	Antisaccade % correct	mean latency
SEPD ($n = 8$)	95.9 (3.5)	52.4 (27.4)	0.179 (0.043)	30.5 (22.5)	0.310 (0.075)
Dyslexia ($n = 5$)	99.1 (1.8)	56.5 (22.3)	0.204 (0.045)	73.2 (15.0)	0.300 (0.057)
normal ($n = 6$)	90.1 (10.3)	75.7 (23.3)	0.193 (0.049)	75.7 (16.1)	0.250 (0.045)
Omnibus F	(2,12) 2.1	(2,16) 2.4	(2,16) 0.69	(2,16) 13.87	(2,16) 2.13
p	0.1606	0.1259	0.5144	0.0003**	0.1561
SEPD *vs* normal					
F	1.868	4.429	0.475	21.581	3.771
p	0.1967	0.0515*	0.5006	0.0003**	0.0725*
SEPD *vs* dyslexia					
F	0.459	0.124	1.328	17.246	0.099
p	0.5110	0.7296	0.2661	0.0007**	0.7575*
Dyslexia *vs* normal					
F	3.945	2.389	0.221	0.055	2.361
p	0.0703*	0.1417	0.6446	0.8183	0.1467

Fixation stability data are missing for three subjects with SEPD and one subject with dyslexia.
*Probability values showing a trend to statistical significance; **significant values.

dyslexics. There were no significant group differences for prosaccade mean latency. In contrast, on antisaccade per cent correct, subjects with SEPD performed significantly worse than both dyslexics and normal controls. Dyslexics did not differ from normal subjects. Subjects with SEPD also showed a trend to longer antisaccade mean latencies. All subject groups showed significant increases in mean latency from prosaccade to antisaccade, but only subjects with SEPD showed a significant decrease in performance accuracy on antisaccade *vs* prosaccade, as measured by per cent correct (SEPD $t = 2.697$, $p = 0.0308$; dyslexia $t = -1.380$, $p = 0.2397$; normal $t = 0.080$, $p = 0.394$).

Neuropsychological measures of attention: The only attentional measures administered to all dyslexic and subjects with SEPD were tests of immediate span. Dyslexics performed significantly better than subjects with SEPD on visual span forward ($F(1,11) = 7.256$, $p = 0.0209$) but were not different in the backward condition ($F(1,11) = 1.289$, $p = 0.2803$). In contrast, subjects with SEPD performed significantly better than dyslexics on digit span forward ($F(1,11) = 6.098$, $p = 0.0312$) and showed a trend to be better on digit span backward ($F(1,11) = 3.857$, $p = 0.0753$).

Discussion

Subjects with SEPD showed deficits in spatially directed attention relative to dyslexic and normal controls. subjects with SEPD did not differ from controls in oculomotor function or in maintaining focused attention. They were less accurate than normals in making simple, reflexive shifts of attention but did not differ from dyslexics. The most striking finding is that subjects with SEPD were markedly deficient in the inhibition of reflexive shifts of attention on antisaccade compared with both control groups and with their own performance on prosaccade.

This pattern of deficient antisaccade but relatively intact prosaccade performance has been demonstrated in patients with lesions of the frontal lobes while those with parietal lobe lesions show the opposite pattern.[18] A recent positron emission tomography study demonstrated that the frontal eye fields were significantly more activated in antisaccade versus prosaccade.[19] These studies implicate the prefrontal cortex as the primary cortical area for inhibiting reflexive saccades. In contrast to parietal lobe injury, damage to prefrontal regions does not appear to disrupt the latency or accuracy of visually guided reflexive saccades,[18] nor does prefrontal damage impair the maintenance of fixation in the absence of distraction.[20] Thus, the pattern of performance of subjects with SEPD can be considered consistent with dysfunction of the prefrontal component of the right hemisphere dominant network for spatially directed attention.

Patients with right hemisphere infarcts consistently demonstrate disruptions in visual attention, including left hemispatial neglect.[5,6] Left hemispatial neglect has also been demonstrated in children with unilateral right hemisphere damage in infancy and with attention deficit disorder.[21,22] There is anecdotal evidence of left hemispatial neglect in SEPD.[1] In this study subjects with SEPD showed no evidence of neglect on a pencil and paper target cancellation test nor were there any differences in eye movement performance for targets appearing in the left *vs* right visual fields. This suggests that left hemispatial neglect is unlikely to account for their deficient performance on the eye movement protocols.

Both learning-disabled groups showed attention deficits on standard clinical neuropsychological tests. Performance on tests of immediate span of attention distinguished between groups, with subjects with SEPD performing worse than dyslexics with visual sequences but better with digits. Most clinical neuropsychological measures of attention are multidimensional and do not adequately delineate the exact nature or specific neuroanatomical substrate of attentional disturbance. In contrast, performance on a task of spatially directed attention as measured by eye movements discriminated subjects with SEPD from both normal individuals and dyslexics, and the pattern of findings suggested a specific neuroanatomical substrate. This suggests that eye movements may serve as a sensitive, reliable and objective physiologically based marker for developmental disorders affecting spatially directed attention. The measurement of eye movements might also aid in the delineation of neuroanatomically valid subtypes of developmental disorders.

Most research on specific learning disabilities has focused on dyslexia, which is associated with both gross and cytoarchitectonic abnormalities disproportionately affecting the left hemisphere.[23] Dyslexia interferes with a wide range of language-related skills, particularly reading. SEPD, in contrast, presumably arises from developmental abnormalities disproportionately affecting the right hemisphere, resulting in its failure to support the adequate development of the cognitive, behavioral and emotional functions it normally subserves.[1,2] The current findings are consistent with evidence linking SEPD to right hemisphere dysfunction and, in particular, to dysfunction of the prefrontal component of the right hemisphere dominant network for spatially directed attention. We speculate that a primary deficit in spatially directed attention could adversely affect the devel-

opment of other social and cognitive skills and, on this basis, might contribute to the other clinical features of SEPD. For example, visual attention deficits could contribute to impairments in visuospatial skills, visuoconstructive ability and receptive and productive aspects of paralinguistic communication involving eye contact, gesture and facial expression. The relationship between the observed deficits in spatially directed attention and other features of SEPD has not been studied and has important implications for understanding the etiology and neuroanatomical basis of this syndrome.

The primary limitation of the current study is the relatively small sample sizes. Although methodological differences in eye movement measurement preclude direct comparison, a previous study of 332 normal and non-neurological patient control subjects, aged 15–89 years, suggested that antisaccade error scores of ⩾ 30% could be considered abnormal.[24] By this criterion, the mean antisaccade performance was abnormal in our SEPD group but not in our dyslexic or normal control groups. While the SEPD group was quite similar to samples described previously,[1,2] the dyslexic group contained a disproportionate number of females and was older than the SEPD subjects. Although we have no reason to expect that age or sex would be associated with antisaccade performance within the range of ages of our subjects,[24] this cannot be ruled out as contributing to the findings. Finally, our samples of adults and adolescents with neurodevelopmental disorders may not be representative of those who come to attention for these conditions earlier in life.

Conclusion

Subjects with SEPD showed a specific deficit in inhibiting reflexive shifts of visual attention and gaze on an antisaccade eye movement protocol. This suggests that they have dysfunction of the prefrontal component of the right hemisphere dominant network for spatially directed attention. A primary deficit in visual attention may adversely affect the development of social and cognitive abilities that are deficient in SEPD.

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