

The Neural Basis of Hyperlexic Reading: An fMRI Case Study

Case Study

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Summary

Children with autism spectrum disorders in very rare cases display surprisingly advanced “hyperlexic” reading skills. Using functional magnetic resonance imaging (fMRI), we studied the neural basis of this precocious reading ability in a 9-year-old hyperlexic boy who reads 6 years in advance of his age. During covert reading, he demonstrated greater activity in the left inferior frontal and superior temporal cortices than both chronological age- and reading age-matched controls. Activity in the right inferior temporal sulcus was greater when compared to reading age-matched controls. These findings suggest that precocious reading is brought about by simultaneously drawing on both left hemisphere phonological and right hemisphere visual systems, reconciling the two prevailing, but seemingly contradictory, single hemisphere theories of hyperlexia. Hyperlexic reading is therefore associated with hyperactivation of the left superior temporal cortex, much in the same way as developmental dyslexia is associated with hypoactivation of this area.

Introduction

The neurobiological basis of reading has been studied in typically developing children (Gaillard et al., 2001, 2003; Schlaggar et al., 2002; Simos et al., 2001; Turkeltaub et al., 2003) and those with disabilities, such as developmental dyslexia (Georgiewa et al., 1999, 2002; Shaywitz et al., 2002; Simos et al., 2000a; Temple et al., 2001). However, little is known about the neural mechanisms of precocious reading. Children with autism spectrum disorders (ASD) in some rare cases display surprisingly advanced reading skills. Despite their severe expressive and receptive language difficulties, these children may accurately identify printed words as young as 18 months of age in the absence of any explicit instruction (Sparks, 1995). This ability, which would likely surprise any parent, is even more extraordinary given that many of these children begin reading before mastering spoken language, and sometimes before speaking at all (Cobrinik, 1982; Elliott and Needleman, 1976; Goldberg and Rothermel, 1984; Healy et al., 1982). Kan-

ner noted the occurrence of this phenomenon when first describing and defining autism (Kanner, 1943), and in 1967, Silberberg and Silberberg defined the term “hyperlexia” to describe children who read at levels beyond those expected for their mental age in the face of disordered oral communication (Silberberg and Silberberg, 1967). Over the ensuing decades of research, three consistent features of hyperlexia have emerged: (1) the presence of a developmental disorder of communication, most commonly an autism spectrum disorder (Healy et al., 1982); (2) acquisition of reading skill prior to age five without explicit instruction (Aram, 1997; Nation, 1999); and (3) advanced word recognition ability relative to mental age, with reading comprehension on par with verbal ability (Burd and Kerbeshian, 1989; Glosser et al., 1996; Goldberg and Rothermel, 1984; Huttenlocher and Huttenlocher, 1973; Temple, 1990; Welsh et al., 1987; Whitehouse and Harris, 1984). Reliable prevalence estimates are not available for hyperlexia, but one population-based study identified four hyperlexic children among a group of 66 with ASD (Burd et al., 1985). Based on a recent epidemiological study of ASD (Yeargin-Allsopp et al., 2003), this suggests a prevalence of 2.2/10,000 for hyperlexia in the general population.

Although hyperlexic children may not comprehend all that they read, print can still become an important route by which they communicate because attention to text is more reliable than attention to voice (Aram, 1997; Kistner et al., 1988). In fact, outcomes for verbal ability and IQ are better for autistic children with hyperlexia than for other autistic children (Burd et al., 1986; Fisher et al., 1988), possibly because reading provides an additional route for communication and socialization (Kistner et al., 1988). Gaining insights into the neurobiological basis of reading in hyperlexic children will be a crucial step to understanding this disorder and may lead to the development of remediation strategies for autism.

Neuropsychological investigations of hyperlexic reading have explored a variety of hypotheses to account for precocious reading and have reached diverse conclusions. Some of these discrepancies are due, in part, to the absence of control subjects and differences in subject inclusion criteria (Burd and Kerbeshian, 1985; Elliott and Needleman, 1976; Goldberg and Rothermel, 1984; Healy et al., 1982; Kistner et al., 1988; Richman and Wood, 2002; Temple, 1990; Welsh et al., 1987; Whitehouse and Harris, 1984). One prevailing theory posits that precocious reading can be explained by an advantage in visual configural analysis. This mechanism was first proposed by Cobrinik (1982) based on evidence that hyperlexic children recognized visually degraded words more easily than controls. Cohen et al. (1997) also provided evidence supporting a visual pattern recognition theory, demonstrating that a group of children with specific language impairment and hyperlexia performed better on tests of visual perceptual skills than specific language-impaired children without hyperlexia. In contrast to the visual theory, Goldberg (1987) proposed that hyperlexia is an example of a savant ability, based on an advantage for declarative over procedural

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memory systems. Likewise, Sparks (1995) concluded that hyperlexic children use rote orthographic memory to read.

However, neither the visual nor the rote memory theory can account for the ability of many hyperlexic children to decode nonwords, a process that necessitates phonological assembly either by analogy to real words or by application of grapheme-to-phoneme conversion rules (Frith and Snowling, 1983; Glosser et al., 1996, 1997; Goldberg and Rothermel, 1984; Healy et al., 1982; Seymour and Evans, 1992; Siegel, 1984; Temple, 1990). In contrast to the nonphonological hypotheses, Welsh et al. (1987) concluded that hyperlexia was based on a phonological advantage used for decoding by grapheme-to-phoneme conversion, rather than direct lexical access. Healy (1982) and Temple (1990) agreed that hyperlexic reading relied on phonological processing but suggested that no unusual strategies were applied and that reading skill acquisition likely followed a typical, but compressed, sequence, including progression from iconic recognition to alphabetic-based phonological decoding to direct lexical processing (Ehri, 1999; Frith, 1985; Høien and Lundberg, 1988). Children who exhibit good phonemic sensitivity prior to attending school go on to be good readers (Bradley and Bryant, 1983) and continue to enhance their phonemic awareness skills through their reading experience (Wagner and Torgesen, 1987). It has been proposed that good expressive and receptive language skills play an important role in developing phonemic awareness (Catts et al., 2002). However, a reversal in the emergence of oral language and phonemic awareness skills in hyperlexic children suggests that phonemic awareness may operate independently from general language ability.

Neurophysiological data would likely help to reconcile the discrepant theories of hyperlexia presented above. To date, the neural basis of reading in hyperlexia remains unexplored. Some cases of hyperlexia have revealed abnormal EEG patterns (Aaron et al., 1990; Elliott and Needleman, 1976; Glosser et al., 1996; Goldberg and Rothermel, 1984; Mehegan and Dreifuss, 1972), but the patterns of abnormal electrical activity have differed between studies. Furthermore, cases with normal EEG findings have also been reported (Goldberg and Rothermel, 1984; Huttenlocher and Huttenlocher, 1973). In the absence of neurophysiological information on hyperlexic reading, neural models of hyperlexia have followed from neuropsychological findings. In support of his visual pattern recognition explanation of hyperlexic reading, Cobrinik (1982) proposed that a right hemisphere-mediated visual configural analysis advantage accounted for precocious reading (Patti and Lupinetti, 1993; Siegel, 1984). In contrast, Welsh et al. (1987) demonstrated a preference for phonological decoding over direct lexical access and proposed that brain systems for phonological decoding hypertrophied to compensate for impairments in other communication systems. Based on current neuroanatomical models of reading, this theory would predict hyperdevelopment of the left hemisphere inferior frontal gyrus and posterior superior temporal cortex (Price, 2000; Pugh et al., 1996a, 2001). Richman and Wood (2002) reconciled the right hemisphere and left hemisphere hypotheses, positing that

hyperlexic children with verbal learning disorders rely on right hemisphere visual association cortex for reading, while nonverbal learning-disordered hyperlexics rely on hypertrophic left hemisphere language systems for reading.

This study was undertaken to provide the first direct examination of the neural basis of reading in hyperlexia, and specifically to test the right and left hemisphere models of hyperlexia discussed above. A recent normative developmental study of reading acquisition utilized functional magnetic resonance imaging (fMRI) to demonstrate that young readers rely on left temporoparietal cortex for word processing and that acquisition of reading skill is associated with increasing activity in the left inferior frontal gyrus and middle temporal gyrus and decreasing activity in the right extrastriate cortex (Turkeltaub et al., 2003). Using identical methods as those employed in this normative study, we present functional brain imaging data on a 9-year-old high-functioning hyperlexic boy, referred to here as Ethan. We directly compare Ethan's brain activity during visual processing of words to two groups of healthy controls: (1) a chronological age-matched group to control for developmental level, and (2) a reading age-matched group to control for text exposure and reading experience. Using the same experimental procedures as those of an existing normative data set also allowed interpretation of Ethan's hyperlexic reading mechanisms in relation to the normal neurodevelopmental changes associated with learning to read. Elucidating the neural basis of reading in hyperlexia will not only shed light on the neurobiology of reading in the context of poor language and communication skills, but will potentially open avenues for identifying alternative routes for reading in children with developmental reading disabilities.

Results

Case History

A reliable history was obtained from Ethan's mother, who also provided medical records, county services records, and home videos from ages 1 to 6 years. Ethan was born by cesarean section to a 42-year-old mother following an uncomplicated 42-week pregnancy. There was no family history of diagnosed neurological or learning disorders. Ethan weighed 10 lbs 2 oz at birth and measured 22 inches in length; height and weight remained above the 90th percentile throughout development, with proportionate head circumference. The only significant illnesses were multiple ear infections from ages 1-0 to 5-0 (years-months; all ages are hereafter reported in this format).

Motor milestones were normal, but hypotonia was noted and subsequent evaluations revealed gross and fine motor deficits (standardized fine motor score of 65 on the Peabody Developmental Motor Scales at age 2-3). Ethan's mother reported no history of motor stereotypies, but a neurologist's report from age 1-6 mentions rolling of the head from side to side, a behavior also present in home video at age 4-0.

At age 1-4, Ethan's mother noted that he didn't seem to comprehend things she said to him, even when she used nonverbal cues. He also was not speaking or using

gestures such as waving goodbye. Home video of Ethan at age 1-1 revealed little response to speech, no spoken words, and very little babble. Ethan's mother also noted differences in the quality of his social interactions. Although generally "happy" and "passive," he displayed limited attachment to his parents, weak eye contact, little interest in other children, and, later, limited pretend play. A developmental evaluation at age 1-7 confirmed deficits in receptive and expressive language as well as verbal imitation and symbolic play.

He subsequently began speech and occupational therapy. Normal hearing was confirmed, and known genetic syndromes were ruled out, although coarse facies were noted. At age 2-6, Ethan had still not spoken his first word and was diagnosed by a neurologist with pervasive developmental disorder-not otherwise specified (PDD-NOS). He began home-based Lovaas behavioral intervention (Lovaas and Smith, 1989) for 25 to 30 hr per week, which continued until age seven. Speech therapy continues to date. At age 3-6, Ethan's first spoken word was one that he read aloud. His first meaningful use of words and word combinations was at 4 years, and spontaneous purposeful use of speech emerged between ages 4-6 and 5-0. Speech was apraxic, with volume dysmodulation, pronoun reversals, and difficulties with reciprocal conversation. Immediate echolalia was infrequent, but delayed echolalia (use of memorized phrases) formed a major part of speech.

Despite his language difficulties, Ethan demonstrated intense interest in text prior to 2 years of age. A home video from his first birthday party (at age 1-1) revealed extended periods in which he scanned magazines, while, behind him, other children played with toys near their parents. A developmental evaluation at age 1-7 also mentions his interest in books. At about age 2-6, without prompting or instruction, Ethan placed letter blocks in alphabetic order, matching upper- and lower-case letters. Prior to three years, he corrected his mother when she pointed to the wrong line of text while reading, and subsequently pointed to words that she read aloud. After speech emerged, Ethan demonstrated correct pronunciations of written words. He preferred nonfiction books, especially about trains, but would read any text available, including street signs, children's dictionaries, and babysitters' textbooks.

At age 4-6, Ethan received the following age equivalent scores on these Vineland Adaptive Behavior Scales: Motor: Gross, 3-1, and Fine, 3-6; Socialization: Interpersonal Relationships, 1-11, and Play and Leisure Time, 1-5; and Communication: Receptive, 3-11, Expressive, 2-7, and Written, 6-4.

We first evaluated Ethan at age 5-10, and nearly annually thereafter. At the first testing session, he was cooperative and pleasant, although poor eye contact, expressive language difficulties, and distractibility were evident. His reading was rapid, with some disregard for punctuation, skipping of words, and attempting to pronounce words while taking breaths. Without repeated prompting, Ethan commonly reverted to silent reading over the course of a passage. However, despite this somewhat compulsive and rushed reading style, some comprehension of text was evident. Since his first evaluation in our research program, Ethan's social and language skills have improved, as has his reading ability. Now at age

10-7, Ethan is highly social, although his overtures are unusual and often inappropriate. His speech is somewhat scripted as well, with rhythmic prosody and volume dysmodulation; he has difficulty with reciprocal conversation. He currently attends the 4th grade of a public elementary school, with the assistance of an aide, and has recently excelled in learning to read Hebrew phonetically.

Psycho-Educational Testing

Scores of neuropsychological assessments are presented in Table 1. Scores on the Wechsler Intelligence Scale for Children, 3rd Edition (WISC) (Wechsler, 1991) administered at ages 6-2 and 10-7 are compared in Figure 1. Several WISC subtest scores "normalized" over that period—Arithmetic, Picture Completion, and Coding—possibly suggesting maturation of fine motor skill and attentional control. The more recent WISC yielded a Full Scale IQ in the superior range, and scatter within the verbal domain (from 7 to 19, where the mean is 10 and the standard deviation is 3). Strengths were in acquired information, abstract verbal reasoning, construction and organization, and attention to detail. A notable weakness remains on a measure of practical knowledge and social judgment (comprehension score of 7), and fine motor coordination, while improved to the normal range, is his weakest timed subtest (coding score of 10).

At age 10-7, there was an advantage for rote verbal learning and memory (Rey Auditory Verbal Learning free recall at the 95th percentile) compared to figure memory (Rey-Osterreith Complex Figure immediate and delayed recall at the 60th and 63rd percentile, respectively). Learning of the Rey word list was similar to that of most students Ethan's age in showing primacy and recency effects for the first two trials with "filling in" of the middle words over the final three trials, ultimately achieving a perfect score with no loss after a distracter trial.

At ages 5-5 and 9-9, Ethan's scores on tests of single word reading, novel word decoding, passage fluency, and spelling were all several years above expectations based on age and IQ. Scores on tests of phonological awareness were high as well. In contrast, reading comprehension scores were somewhat variable. At age 9-9, both the Woodcock-Johnson III and Gray Oral Reading Test indicated comprehension somewhat advanced for Ethan's age, but still 4-5 years behind his reading ability. Scores on oral receptive language measures (Woodcock-Johnson Oral Comprehension and Understanding Directions) were commensurate with reading ability. This was surprising given Ethan's history of language impairment and his continuing difficulties with oral communication. However, most of his current difficulties are with pragmatic aspects of language not measured by the subtests administered.

fMRI Task Performance

Brain activity during reading was measured using a "covert reading" task in which subjects detect the presence of a visual feature (tall letters) within both words and matched false font strings (Price et al., 1996). This task engages the same neural systems as overt reading tasks and reduces effort-related differences in reading activ-

Table 1. Psycho-Educational Assessment Scores

Test	Ethan at Initial Testing	Ethan at fMRI Acquisition	Chronological Age-Matched Controls (n = 9)	Reading Age-Matched Controls (n = 8)
Age (years-months)	5-11	9-9	9-5 (0-7)	11-8 (3-10)
Full Scale IQ (ss) ^a	109 ^b	127 ^c	126.3 (16.4)	119.8 (13.8)
Verbal IQ (ss)	104 ^b	121 ^c	129.2 (11.3)	123.3 (10.2)
Performance IQ (ss)	113 ^b	130 ^c	117.6 (17.8)	111.9 (16.4)
WJ-Letter/Word ID (age eq.)	8-10	15-1	11-1 (1-11)	14-6 (2-2)
WJ-Word Attack (age eq.)	9-4	16-11	10-4 (2-1)	14-5 (3-2)
WJ-Passage Comprehension (age eq.)	8-7	11-9	10-9 (1-10)	14-5 (6-10)
GORT-Passage (age eq.)	9-4	13-11	11-0 (2-5)	13-4 (3-1)
GORT-Comprehension (age eq.)	6-11	11-1		
Test of Written Spelling-4 (age eq.)		17-6	10-1 (2-4)	13-5 (3-1)
WJ-III-Oral Comprehension (age eq.)		19-0	13-10 (2-5)	14-5 (4-4)
WJ-III-Understanding Dir. (age eq.)		15-0	11-1 (3-9)	15-5 (2-9)
LAC (max = 100)		94	89.1 (12.6)	86.3 (7.8)
RAN-Letter-Number Mean (s)	54.5	19.5	31.6 (5.8)	24.1 (4.6)
RAN-Color-Object Mean (s)	84.5	36.5	51.9 (8.1)	42.8 (9.5)
Digit Span-Forward + Backward (raw)	10	15	12.7 (3.0)	16.8 (4.9)
Manis Exception Words (max = 70)		69	55.4 (8.8)	64.6 (3.1)
Boston Naming (max = 60)		51	43.2 (5.3)	47.8 (3.9)
FAS Verbal Fluency (words/60 s)		29	23.7 (10.6)	29.9 (11.6)
NEPSY Semantic Fluency (words/60 s)		48	33.4 (6.7)	38.1 (11.0)
Purdue Pegboard R+L+Both (pegs/30 s)		32	32.7 (4.5)	37.9 (3.8)
Purdue Pegboard Assembly (pieces/60 s)		27	26.8 (4.2)	30.6 (8.5)
Edinburgh Handed. Inv. (max RH = 100)	88.9		92.4 (10.2)	82.3 (21.7)

The most current available edition of each test was used for all evaluations. Ages and age equivalents are given as years-months. GORT age equivalent was estimated by adding 5 years to the “grade equivalent” scores.

Abbreviations: WJ, Woodcock Johnson; GORT, Gray Oral Reading Test; LAC, Lindamood Auditory Conceptualization; RAN, Rapid Automated Naming.

^aIQs were assessed by Wechsler Intelligence Scale for Children, 3rd edition, for Ethan and Wechsler Abbreviated Scale of Intelligence for controls. ss = standardized score (mean = 100, SD = 15).

^bAssessment was performed at age 6-2.

^cAssessment was performed at age 10-7.

ity, because reading occurs obligatorily without conscious effort (Figure 2, see Experimental Procedures for details). All subjects performed the feature detection task accurately for both word and false font string stimuli (Table 2). Ethan responded more accurately and faster to false font string stimuli than to words. In contrast,

control groups performed the tasks with equal accuracy, but more quickly for words (chronological age-matched: $t(8) = 1.87$, 2-tailed $p < 0.1$; reading age-matched: $t(6) = 3.93$, 2-tailed $p < .01$). Overall, Ethan responded to stimuli more slowly than controls. This is not surprising given his history of motor deficits.

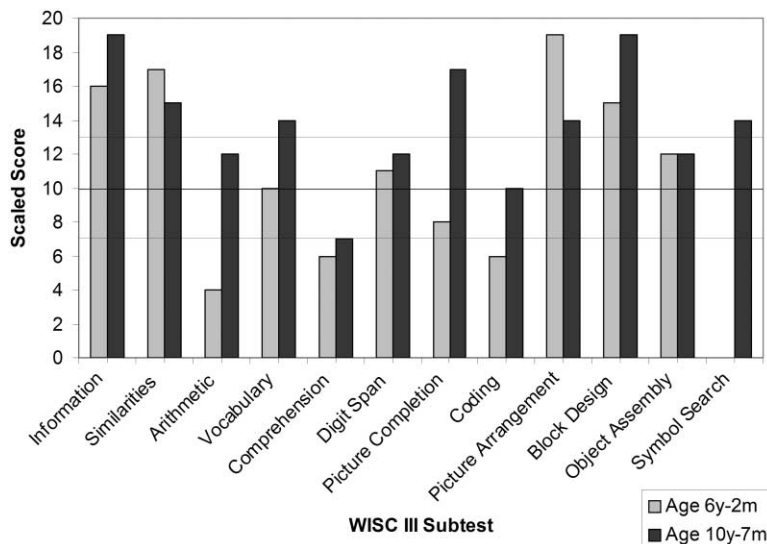


Figure 1. Ethan's Scores on the Wechsler Intelligence Scale for Children, 3rd Edition

Scores depict the scatter of Ethan's ability among the subtests at ages 6-2 and 10-7. A large increase in IQ was observed between the testing sessions, largely due to improved compliance and communication, but the pattern of scatter remained relatively stable. Comprehension, which measures practical knowledge and social judgment, was the only subtest on which Ethan scored one or more standard deviations below the mean at both testing sessions. Standardized scores have a population mean of 100 and a standard deviation of 15. Scaled scores have a population mean of 10 and a standard deviation of 3.

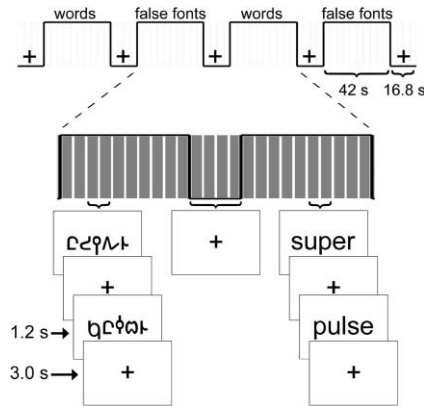


Figure 2. Feature Detection/Covert Reading fMRI Task
Alternating epochs of crosshair fixation (+), words, and false font strings were presented. Not shown here is a 16.8 s epoch at the beginning of each run to allow for longitudinal magnetization equilibration. Four whole-brain volumes were acquired during fixation epochs, whereas 10 volumes were acquired during word and false font string epochs. Subjects pressed a button held in their right hand if stimuli contained ascenders or “tall letters” and a button held in their left hand if they did not. Here, “super” would be given a “no” response, as would the first false font string. “Pulse” would be given a “yes,” as would the second false font string. Two runs were collected in this manner for a total of 40 whole-brain EPI volumes per task condition (words, false font strings, fixation). Previous studies have shown that the contrast of words versus false font strings activates typical reading circuitry due to the obligatory “covert reading” of words (Price et al., 1996; Turkeltaub et al., 2003).

On a forced choice recognition posttest administered to confirm covert processing of words, Ethan correctly recognized 36 out of 40 words presented during scanning, with only one false positive out of the 40 words not presented during scanning (93.8% accuracy, $d' = 3.24$). This score was several standard deviations above the mean for either chronological age- or reading age-matched control groups (Table 2) and was substantially higher than the best performing control subject (82.5% accuracy, $d' = 2.39$). In contrast, Ethan recognized only 28 out of 40 false font strings presented during scanning, with 28 false positives (50.0% accuracy, $d' = 0.00$). Likewise, recognition of false font strings was at chance for both chronological age- and reading age-matched control groups.

fMRI Results
Ethan

Single-subject analysis of the hyperlexic child during covert word reading revealed activity in several left fron-

tal regions, namely the medial superior frontal gyrus, the inferior frontal gyrus (BA 44/45), and the superior frontal sulcus (BA 9; Figure 3, Table 3). Ethan also activated a long strip of the left posterior superior temporal sulcus/gyrus (BA21/22). While the right frontal lobe was largely silent, a small area of the right superior temporal sulcus was active. Other right hemisphere cortical areas were active also, including the central sulcus, the insula, the posterior cingulate gyrus, and the calcarine sulcus. Subcortically, the left thalamus and a lateral area of right cerebellar cortex were active.

Ethan versus Chronological Age-Matched Controls

In a mixed-effects SPM Compare Groups analysis, Ethan demonstrated greater activity than age-matched controls in left lateralized cortical regions, including the posterior inferior frontal cortex (posterior inferior frontal sulcus and the precentral sulcus bounding the pars triangularis) and the superior temporal sulcus/gyrus (Figure 4, Table 4). Precentral sulcus activity was also observed near the right superior convexity. On the medial surface, Ethan activated the left anterior cingulate sulcus and the right posterior paracentral lobule to a greater degree than controls. However, all nine chronological age-matched control subjects demonstrated peaks of activity within 15 mm of the anterior cingulate gyrus activation, and the mean Z score of these peaks was similar to Ethan’s peak Z score. Thus, in contrast to the other results above, this last finding likely reflects variability in the location of anterior cingulate gyrus activity among controls, rather than a difference in magnitude of activity between Ethan and controls. Finally, Ethan demonstrated less activity relative to chronological age-matched controls in a few ventral areas of the brain, including the left parahippocampal gyrus and the pons.

Ethan versus Reading Age-Matched Controls

Ethan activated areas of the left inferior frontal and superior temporal cortices to a greater degree than older, reading age-matched controls (Figure 5, Table 4). These differences were similar to those observed in the comparison to chronological age-matched controls described above. Left inferior frontal activity lay in the inferior frontal gyrus and the precentral sulcus bounding the pars triangularis. Greater precentral sulcus activity was also observed near the superior convexity. Ethan activated two areas of the superior temporal sulcus/gyrus in excess of reading age-matched controls, one inferior to Heschl’s gyrus (near an area identified in the comparison with chronological age-matched controls) and one just anterior to the ascending ramus. However,

Table 2. fMRI Feature Detection/Covert Reading Task Scores

	Ethan	Chronological Age-Matched	Reading Age-Matched
Words			
fMRI task accuracy (% correct)	90.0	93.1 (7.3)	89.6 (8.0)
fMRI task RT (ms)	1003	879 (128)	770 (43)
Posttest accuracy (% correct)	93.8	61.5 (6.3)	68.6 (7.8)
False font strings			
fMRI task accuracy (% correct)	97.5	92.5 (8.1)	88.2 (10.6)
fMRI task RT (ms)	931	917 (86)	827 (49)
Posttest accuracy (% correct)	50.0	52.6 (5.1)	49.6 (3.1)

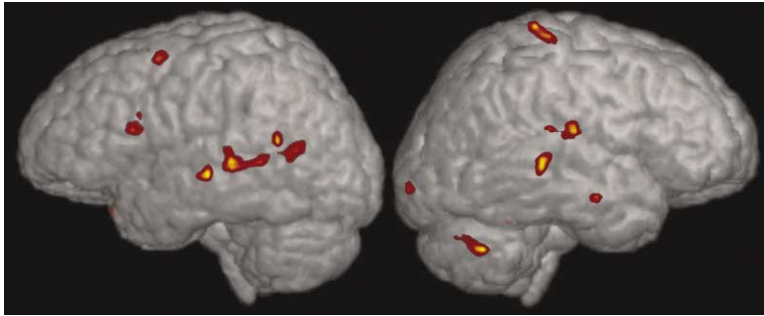


Figure 3. Areas Activated by Ethan during Covert Reading

Ethan demonstrated robust activity in areas commonly associated with reading, including the left inferior frontal gyrus and left lateralized posterior superior temporal cortex. Areas of significant activity ($p < 0.001$, uncorrected) are thresholded at $p < 0.005$ here for ease of visualization. Images are maximum intensity renderings of Ethan's T1-weighted MPRAGE with a penetration distance of 25 mm.

all eight control subjects demonstrated single subject Z maxima within 15 mm of this latter area. In contrast, only six control subjects had Z maxima near the more anterior area (superior temporal sulcus/gyrus), and all six of these maxima were smaller than Ethan's peak (control range = 1.8–3.0; Ethan = 3.4). Unlike the comparison with chronological age-matched controls, Ethan also activated two large areas of the right inferior temporal sulcus to a greater degree than reading age-matched controls. The single subject analysis revealed that Ethan's single subject Z peaks near these regions were relatively small ($Z = 1.94$ – 2.06), but few control subjects demonstrated any activity in these areas at all.

Several brain areas were less active in our hyperlexic subject compared to reading age-matched controls: activity was reduced in the left ventral inferior frontal gyrus, middle frontal gyrus, temporal insula, and hippocampus. Right hemisphere areas of reduced activity included the anterior inferior temporal sulcus, the supramarginal gyrus, and the lingual gyrus.

Ethan versus Controls: Overview

In summary, we observed two clear patterns in Ethan's covert reading activity in comparison to controls: (1) increased activity relative to both control groups in left

hemisphere inferior frontal and posterior superior temporal cortical areas, and (2) increased activity relative to reading age-matched control subjects in right hemisphere inferior temporal cortical areas.

Region-of-Interest (ROI) Analysis

A ROI analysis was performed to verify that the hyperlexic child differentially activated typical mature reading areas and to confirm that the above findings did not reflect small variations in location of activity among control subjects (Table 5). ROIs were determined as clusters of significant activity in a group of 15 normal adult subjects (see Experimental Procedures). Ethan demonstrated activity greater than two standard deviations above the mean of both chronological and reading age-matched control groups in several ROIs. The greatest differences were in ROIs in the left inferior frontal gyrus (BA 44/45), the left superior temporal gyrus (BA 22), the right cerebellum, and the right inferior temporal sulcus (BA 21/37). These results confirm the findings of the voxel-wise analysis demonstrating increased covert reading activity for the hyperlexic subject relative to control subjects in reading-related areas of the left inferior frontal, left superior temporal, and right inferior temporal cortices.

Table 3. Ethan's Brain Activity during Covert Reading

Location	x	y	z	Z Score
Left				
Medial superior frontal gyrus	-8	58	-10	3.12
	-4	54	-14	3.24
Inferior frontal gyrus	-44	20	12	3.14
Inferior frontal sulcus	-32	16	22	3.49
Superior frontal sulcus	-26	12	52	3.35
Superior temporal sulcus/gyrus	-58	-20	-10	3.72
	-60	-32	-4	3.40
	-62	-44	0	3.18
	-44	-52	14	3.32
	-58	-62	8	3.13
Posterior cingulate gyrus	-6	-46	12	3.52
Thalamus	-10	-18	6	3.45
Right				
Orbitofrontal cortex	14	38	-14	3.37
Central sulcus	26	-20	68	3.28
Central sulcus	22	-24	72	3.46
Insula	46	-12	12	3.48
Insula	38	-24	16	3.32
Inferior temporal sulcus	50	-4	-26	3.20
Superior temporal sulcus	52	-30	-4	3.58
Calcarine sulcus	10	-98	-6	3.29
Cerebellum	38	-60	-44	3.80

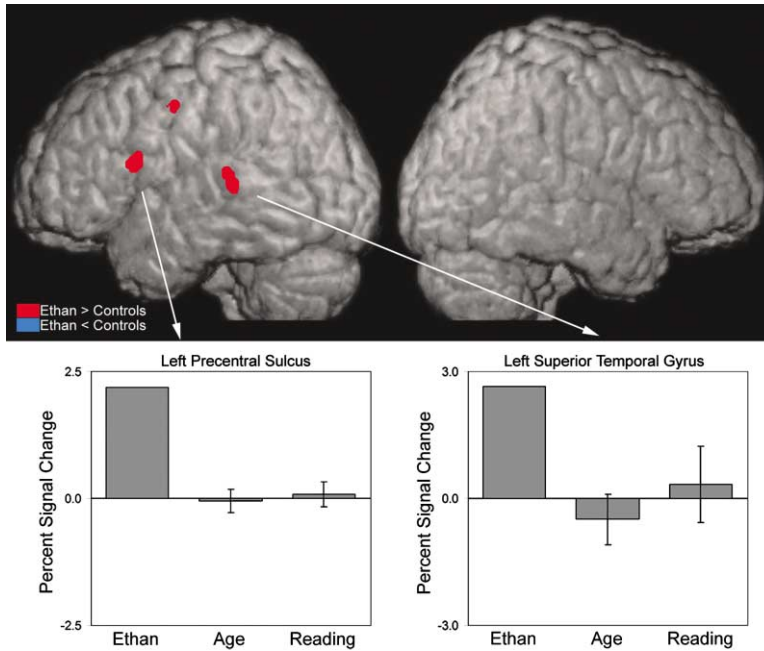


Figure 4. Covert Reading Activity: Ethan versus Chronological Age-Matched Controls

This contrast reveals brain areas that Ethan activates differently from other children of his age group during word processing. Ethan activated the left inferior frontal gyrus, precentral sulcus, and superior temporal cortex to a greater degree than chronological age-matched controls. A complete list of significant areas is given in Table 3. Activity (peak $p < .0001$, extent $p < .001$, 2-tailed, uncorrected) is rendered onto Ethan's T1-weighted MPRAGE spatially normalized to the template provided in SPM99. The penetration distance is 25 mm. The graphs give the average percent signal change for the word versus false font contrast within significant clusters for Ethan, chronological age-matched controls, and reading age-matched controls. Error bars represent the standard deviation for control groups.

Discussion

Previous neuropsychological investigations have proposed two main hypotheses to account for advanced reading in hyperlexia: (1) hypertrophied left hemisphere phonological processing units (Welsh et al., 1987), and (2) use of right hemisphere extrastriate cortex for visual form recognition (Cobrinik, 1982). In contrast to these "single hemisphere" hypotheses, our findings suggest that our hyperlexic subject employs both left hemisphere and right hemisphere mechanisms for precocious reading.

Left Hemisphere in Reading and Phonological Processing

As predicted by the left hemisphere phonological hypertrophy hypothesis of hyperlexia (Welsh et al., 1987), Ethan activated both the left inferior frontal gyrus and the left superior temporal cortex during covert reading to a greater degree than reading age- and chronological age-matched control subjects. These findings were confirmed by the ROI analysis. Furthermore, examination of Ethan's two imaging runs independently revealed within-subject consistency, with foci from both runs contributing to these left hemisphere activations. The left inferior frontal gyrus and superior temporal cortex are commonly implicated in normal adult reading (Fiez et al., 1999; Fiez and Petersen, 1998; Price, 1997, 2000; Price et al., 1996; Pugh et al., 2001; Turkeltaub et al., 2002). Specifically, these areas play a key role in phonological decoding, the translation of printed words to sound units and the assembly of those sound units into phonetic codes (Hagoort et al., 1999; Poldrack et al., 1999; Pugh et al., 1996b). Interestingly, our normative study of reading (using the same fMRI task) revealed that activity in left inferior frontal and superior temporal

cortices was modulated by children's phonemic awareness skills measured outside of the scanner (Turkeltaub et al., 2003). Phonemic awareness is the ability to isolate and manipulate the constituent sounds of words and is causally related to learning in early stages of reading acquisition (Treiman, 2000; Wagner and Torgesen, 1987; Wagner et al., 1993, 1997). In the present study and in Turkeltaub et al. (2003), phonemic awareness was assessed using the Lindamood Auditory Conceptualization test, which requires subjects to represent the number, order, and identity of phonemes by manipulating colored blocks (Lindamood and Lindamood, 1979). Ethan performed this task better than most of the control subjects (Table 1). The fact that Ethan activated left inferior frontal and posterior superior temporal regions even more than children of the same reading ability, along with this behavioral evidence of good phonological ability, indicates a true hyperactivation of phonological systems for reading.

Hyperlexia versus Dyslexia

In contrast with this hyperactivation, adults and children with dyslexia have demonstrated decreased brain activity relative to controls in left temporoparietal cortex during performance of reading-related tasks (for review, see Eden and Moats, 2002; Eden and Zeffiro, 1998). Poor phonological awareness is considered the core deficit in developmental dyslexia (Lyon, 1995); tasks that directly necessitate phonological processing have therefore frequently been employed in brain imaging studies of disabled readers. Studies of adults with dyslexia have included word and letter rhyming, phonological decisions, and nonword reading (Rumsey et al., 1992, 1997; Shaywitz et al., 1998). Investigations of dyslexic children have involved reading real and nonwords and nonword rhyme matching (Shaywitz et al., 2002; Simos et al.,

Table 4. Brain Activity during Covert Reading: Ethan versus Controls

Location	Volume (mm ³)	Peak Z	x	y	z
Ethan > Chronological Age-Matched Controls					
Left					
Anterior cingulate sulcus	384	4.45 ^a	-14	60	2
Inferior frontal sulcus	1256	4.27 ^a	-34	14	26
Precentral sulcus		4.21 ^a	-42	18	14
Superior temporal gyrus/sulcus	320	3.80	-68	-32	8
Right					
Precentral sulcus	264	4.11 ^a	18	-30	70
Posterior paracentral gyrus	216	3.86	10	-54	56
Ethan < Chronological Age-Matched Controls					
Left					
Parahippocampal gyrus	680	4.64 ^a	-22	-2	-39
		4.03	-22	-4	-51
Right					
Pons	240	3.83	0	-18	-38
Ethan > Reading Age-Matched Controls					
Left					
Precentral sulcus	456	3.81	-56	18	21
Inferior frontal gyrus	840	4.25 ^a	-38	14	16
Pons	392	3.91	-6	-8	-28
Precentral sulcus	1520	4.30 ^a	-26	-20	64
		4.22 ^a	-16	-16	58
Parahippocampal gyrus	344	5.07 ^a	-26	-29	-34
Temporal pole	528	4.54 ^a	-26	18	-34
Medulla	704	3.98	-10	-36	-60
Superior temporal sulcus/gyrus	936	4.73 ^a	-68	-38	-5
Superior temporal sulcus	808	4.36 ^a	-62	-60	4
		4.31 ^a	-60	-66	8
Right					
Orbital gyrus	296	3.81	28	28	-11
Precentral sulcus	1864	4.51 ^a	26	-20	70
Transverse temporal gyrus	696	4.62 ^a	52	-24	2
Paracentral gyrus	448	4.02	0	-28	64
Inferior temporal sulcus	1944	4.39 ^a	54	-40	-15
		3.92	40	-66	2
Inferior temporal sulcus	1512	4.78 ^a	51	-68	-4
Ethan < Reading Age-Matched Controls					
Left					
Inferior frontal gyrus	904	4.03	-38	46	-20
Orbital gyrus		3.86	-24	38	-16
Middle frontal gyrus	928	4.22 ^a	-44	16	52
Insula	480	4.25 ^a	-42	-12	-16
Hippocampus	840	4.70 ^a	-20	-14	-34
Hippocampus		3.91	-28	-14	-26
Cerebellum	248	4.37 ^a	-4	-68	-60
Right					
Inferior temporal gyrus	1312	4.12 ^a	34	6	-52
Inferior temporal gyrus		4.06	18	0	-46
Middle temporal gyrus	264	4.06	54	0	-44
Supramarginal gyrus	384	3.98	56	-46	52
Lingual gyrus	344	4.24 ^a	10	-72	-22
Cerebellum	304	3.99	20	-78	-50

^ap < 0.05 after Resel correction for multiple comparisons

2000a, 2000b). Using diverse methodologies (functional MRI, positron emission tomography, and magnetoencephalography), hypoactivity of the left posterior superior temporal cortex has been demonstrated in dyslexic compared to normal readers. Although other regions (including the left inferior frontal gyrus and parietal cortex) are also known to be anomalous in their activity, it is notable that several studies of dyslexic children and adults show hypo-

activity in close spatial proximity to the left hemisphere posterior superior temporal cortex found to be hyperactive in our hyperlexic child (Rumsey et al., 1992; Shaywitz et al., 1998, 2002; Simos et al., 2000a). Two studies have demonstrated this dyslexic hypoactivity using the same covert reading task used in the present study (Brunswick et al., 1999; Paulesu et al., 2001). This dissociation between hyperlexic and dyslexic subjects supports the notion that,

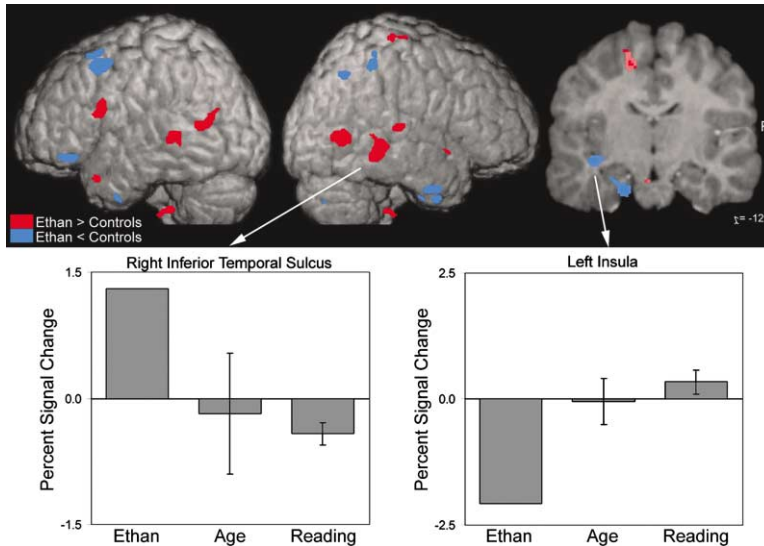


Figure 5. Covert Reading Activity: Ethan versus Reading Age-Matched Controls

This contrast reveals brain areas that Ethan activates differently from children who are older but at the same reading level as Ethan. During word processing Ethan activated the left inferior frontal gyrus, left superior temporal sulcus/gyrus, and right inferior temporal sulcus to a greater degree than reading age-matched controls. He demonstrated less activity than reading age-matched controls in the left insula, left superior frontal gyrus, and right intraparietal sulcus. A complete list of significant areas is given in Table 3. Activity (peak $p < .0001$, extent $p < .001$, 2-tailed, uncorrected) is rendered onto Ethan's T1-weighted MPRAGE spatially normalized to the template provided in SPM99. The penetration distance is 25 mm. The graphs give the average percent signal change for the word versus false font contrast within significant clusters for Ethan, chronological age-matched controls, and reading age-matched controls. Error bars represent the standard deviation for control groups.

at least with regard to left posterior superior temporal cortex, these disorders are “two sides of the same coin” (Snowling, 1987).

This striking correspondence between brain activity and reading status illustrates the importance of the left superior temporal cortex for reading acquisition. Our normative study (Turkeltaub et al., 2003) found this area to be engaged early in the course of reading acquisition and its activity to be modulated by children's phonological skills; however, its activity did not change over the course of normal reading acquisition, as in previous developmental studies (Schlaggar et al., 2002; Shaywitz et al., 2002; Simos et al., 2001). One possible explanation is that the superior temporal cortex contains crossmodal or multisensory neurons, which determine the aptitude of an individual for reading but are not changed by schooling. Thus, left posterior superior temporal cortex activity could be an important predictor of future reading success in young children. Evidence in support of this role as a multisensory brain area has been presented in studies of audiovisual integration of phonemes and graphemes (Rajj et al., 2000), consistent with earlier observations of audio-visual integration reported in animal and human studies (Calvert, 2001).

Reading in the Absence of Oral Language

Remarkably, Ethan's advanced phonological processing emerged despite severe deficits in expressive and receptive language, suggesting that phonological awareness may exist independent of language. Ethan began focusing on text as early as 13 months of age and was able to recognize printed words prior to developing spoken language. During this period, he also experienced significant receptive language difficulties. At this early stage of reading acquisition, it would seem that phonological systems were functioning for decoding print but did not support expressive or receptive speech. One explanation is that the phonological processing system is functionally independent of oral language development, possibly due to its role in audio-visual integration described above.

Another is that right hemisphere visual form recognition systems were primarily responsible for Ethan's reading prior to the development of language, and robust activation of typical phonological systems emerged as receptive and expressive language improved. Brain imaging studies of younger children with hyperlexia will be needed to test these alternative explanations.

Right Hemisphere in Reading

In addition to left hemisphere systems, Ethan also demonstrated greater activity than reading age-matched controls in the right posterior inferior temporal sulcus. This extrastriate region has been implicated in visual form recognition (Tanaka, 1997), and our normative developmental study revealed that children developmentally disengage this area over the course of reading acquisition (Turkeltaub et al., 2003). Young children probably recruit these right extrastriate regions for early phases of reading, during which they use visual patterns or visual context to recognize words (e.g., a small word with a tail is “dog,” a word in a red hexagonal sign is “stop”) (Ehri, 1999; Frith, 1985; Høien and Lundberg, 1988). Then, these areas are likely disengaged as children rely more on letter-to-sound correspondences and less on visual configurational analysis to identify words.

In contrast with this normal developmental pattern, Ethan does not demonstrate disengagement of these right ventral stream areas to the degree that his reading peers do. Rather, he has retained a level of activity in the inferior temporal sulcus commensurate with his age but overly active for his reading ability. Examination of Ethan's brain activity independent of controls reveals modest elevations of maxima within right ventral extrastriate systems. Thus, the contributions of these form-processing areas to Ethan's reading appear unusual relative to other children of comparable reading ability, but not as important as the contributions of left hemisphere phonological systems. These findings indicate that a hyperlexic child can use right hemisphere-mediated visual form recognition systems to

Table 5. ROI Analysis of Brain Activity in Mature Reading Areas: Ethan versus Controls

Location	Chronological Age-Matched Controls						Reading Age-Matched Controls					
	x	y	z	Volume (mm ³)	Ethan % Signal Change	Mean % Signal Change	Ethan vs. Controls: SD from Mean	Ethan vs. Controls: Rank (/10)	Mean % Signal Change	Ethan vs. Controls: SD from Mean	Ethan vs. Controls: Rank (/9)	
Left												
Anterior cingulate gyrus	-16	40	32	832	1.02	-0.04 (0.65)	1.64	1	0.09 (0.29)	3.24	1	
Inferior frontal gyrus (ventral)	-41	40	-11	1008	0.56	-0.22 (0.79)	0.98	2	0.14 (0.4)	1.05	2	
Inferior frontal gyrus (dorsal)	-41	15	7	6000	0.92	0.1 (0.11)	7.68	1	0.19 (0.24)	3.02	1	
Central sulcus	-20	-34	60	488	0.61	0.31 (0.53)	0.56	3	0.2 (0.38)	1.07	2	
Middle temporal gyrus	-54	-8	-17	1216	0.30	-0.25 (0.47)	1.17	3	0.09 (0.44)	0.47	4	
Superior temporal gyrus	-60	-37	4	1328	1.26	0.06 (0.26)	4.60	1	0.49 (0.31)	2.47	1	
Right												
Medial superior frontal gyrus	7	5	59	328	0.91	0.12 (0.3)	2.61	1	-0.06 (0.41)	2.39	1	
Cingulate gyrus	11	2	38	1904	1.08	0.07 (0.26)	3.85	1	0.25 (0.41)	2.05	1	
Precentral gyrus	42	-12	61	464	-0.94	-0.37 (0.8)	-0.72	8	-0.31 (0.73)	-0.87	7	
Middle temporal gyrus	65	-17	-12	600	0.57	-0.25 (0.49)	1.69	1	0.02 (0.35)	1.57	2	
Inferior temporal sulcus	53	-29	-15	576	2.14	0.03 (0.84)	2.52	1	0.04 (0.48)	4.42	1	
Postcentral gyrus	21	-39	68	456	0.95	-0.15 (0.53)	2.06	1	0.22 (0.42)	1.75	1	
Inferior parietal lobule	60	-47	29	3016	0.08	0.17 (0.68)	-0.12	7	0.65 (0.43)	-1.32	9	
Cerebellum	33	-69	-47	1456	1.43	-0.17 (0.35)	4.57	1	-0.09 (0.71)	2.13	1	

Each ROI derived from the group map of 15 adult subjects is listed with location, mean Talairach x, y, and z coordinates, and the volume of the ROI. % signal change refers to the mean word-versus-false font string percent difference within the ROI. The standard deviation of this value across the control subjects is given in parentheses. Rank refers to Ethan's place in a list of the subject's percent signal change ordered from highest to lowest (e.g., a rank of 1 indicates that Ethan's average percent signal change in the ROI was greater than that of all the control subjects).

support left hemisphere phonological systems during reading. Further, these findings clarify the relationship between right hemisphere ventral extrastriate activity and normal reading acquisition. Although previous evidence suggests that normal reading-related right inferotemporal activity decreases over the course of schooling (Turkeltaub et al., 2003), Ethan's high activity in that region demonstrates that advanced reading can be attained without this developmental disengagement. Therefore, age-related decreases of right inferotemporal activation may not be causally related to reading acquisition, but rather may reflect decreased reliance on visual form during mature reading.

Hyperlexia and Declarative Memory

Some researchers have proposed that hyperlexic reading is performed via exceptional declarative memory systems (Goldberg, 1987) that support reading via rote recognition of known words or identification of unknown words by analogy to known ones. Ethan's high scores on the covert reading posttest ($d' = 3.24$, see Table 2) and the Rey Auditory Verbal Learning test (recall at the 95th percentile) indicate unusual declarative memory ability for words. However, a general declarative memory advantage is not indicated by his typical performance for nonlexical stimuli on both the false font recognition posttest ($d' = 0.00$) and the Rey-Osterreith Complex Figure Test (delayed recall at the 63rd percentile). Rather, the same advanced phonological and visual processors active during reading might provide cues to support efficient encoding and retrieval of words from declarative memory. Further, given that Ethan's brain activity during covert reading was reduced relative to controls in several areas of the hippocampal formation, the fMRI data do not support a memory-based mechanism for reading.

Neuronal Reorganization versus Strategy

Multiple mechanisms could account for the altered neural signature for reading in hyperlexia. Given Ethan's history of autism spectrum disorder and early reading acquisition, it is tempting to attribute brain activity differences to reorganization of the neural circuitry supporting reading. Early neural anomalies could developmentally drive reorganization. Tirosh and Canby (1993) noted advantages for hyperlexic children in graphesthesia, stereognosis, and eye-tracking compared to other autistic children and proposed that hyperlexia emerges when pervasive neural impairment results in hypertrophy of specific spared systems. Perturbations in certain processing systems due to a developmental cognitive disorder could result in a diversion toward intact visual form processing and phonological decoding systems. In early childhood, sparing of systems capable of processing text might drive an increased affinity toward print. Over time, exposure to text and focus of attention toward specific aspects of reading could result in hypertrophy of phonological decoding systems.

Alternatively, these findings are also compatible with differential allocation of attentional resources toward particular parts of an intact, normal reading system. Ethan's brain activity during covert reading was reduced relative to controls in some brain regions associated with reading and word retrieval, including the left insula and medial

temporal structures. Likewise, his reading comprehension ability falls in the average range, despite his advanced decoding rate and accuracy and high IQ. Thus, differences in Ethan's brain activity could reflect diversion of attentional resources from semantic aspects of reading to phonological and visual aspects. Future brain imaging studies investigating semantic processing in hyperlexic children may shed light on this question.

Summary

Using fMRI, we examined the neural basis of reading in hyperlexia in a 9-year-old boy. During covert reading he was found to engage left hemisphere phonological decoding systems as well as right hemisphere visual form recognition systems to a greater degree than chronological age- and reading age-matched controls. In contrast to the prevailing single hemisphere theories of hyperlexia, these findings indicate that hyperlexic reading is brought about by simultaneously drawing on both left hemisphere phonological and right hemisphere visual systems. These findings demonstrate for the first time that precocious reading is associated with hyperactivation of left posterior superior temporal cortex, just as impaired reading in dyslexia is associated with hypoactivation of regions surrounding the posterior superior temporal cortex. Continued study of brain function in hyperlexia may reveal alternative mechanisms for reading remediation for children with developmental disorders of cognition.

Experimental Procedures

Subjects

We studied one male monolingual right-handed hyperlexic subject (Ethan) and 17 healthy monolingual right-handed control subjects. At the time of MRI data acquisition, Ethan was 9 years and 9 months of age. Control subjects were matched to Ethan on either chronological age (± 1 year, $n = 9$) or reading ability (± 5 words on the Woodcock-Johnson Letter Word I.D., $n = 8$); one subject qualified for both control groups. Both control groups were also matched to Ethan on Full Scale I.Q. (Table 1). Control subjects had participated in a normative study on brain development (Turkeltaub et al., 2003) and were originally recruited through flyers posted at Georgetown University and sent to parents through private schools in the Washington, DC, metropolitan area. The research participants were studied at the Georgetown University Medical Center's General Clinical Research Center. All subjects were screened for substance abuse, presence of metal objects in their bodies, claustrophobia, and personal or family history of neurological, psychological, and learning disorders via a parental phone questionnaire. A clinical neuropsychologist (D.L.F.) ruled out reading disorders on the basis of a psycho-educational assessment battery including commonly used standardized measures of I.Q., word identification, decoding, passage reading, reading and oral comprehension, phonological processing, confrontation naming, and gross and fine motor coordination (Flowers et al., 2001).

fMRI Methods

Each subject completed the study protocol in three sessions over a 3 week period. Each session lasted approximately 2 hours, and subjects were given frequent breaks. The first and third sessions consisted of neuropsychological testing; functional MRI data acquisition occurred during the second session. Children were motivated by prizes, stamps, and stickers given to indicate their progress through the protocol.

fMRI Task

To measure brain activity during reading, we used a word-processing task developed by Price and colleagues (Price et al., 1996) in which subjects read "covertly" by detecting the presence of a visual feature (tall letters) within both words and matched false font

strings (Figure 2). Single, low-frequency (Kucera-Fancis frequency = 8.1, SD = 6.1), 5-letter words were presented. Subjects pressed either a button held in their right hand if they detected one or more ascenders in the word, or else a button held in their left hand if they did not. Ascenders were defined as letters that rise above the level of others (e.g., t f h) or “tall letters.” Accuracy and response time were recorded. Half of the word stimuli contained ascenders, and, to avoid confusion, no words contained the letters “i” or “j.” Each stimulus was presented for 1.2 s, followed by a fixation crosshair for 3 s. Epochs of this task alternated with the same ascender detection task performed on false font strings (e.g., $\delta\lambda\lambda\epsilon\epsilon$), which matched stimulus words for number of characters, visual angle subtending, location of ascenders and descenders, and pattern of repeating letters. Subjects could not decode false font strings, as no one-to-one mapping existed between false font characters and English letters. Words were presented in black Arial font on a white background. The false font was generated by altering the Arial font to create unfamiliar characters.

Although subjects are not explicitly required to read word stimuli in order to perform the feature detection task, reading occurs without conscious effort as an obligatory process. This obligatory processing, in the present study termed “covert reading,” results in activation of the same neural reading circuitry engaged by explicit reading tasks (Paulesu et al., 2000; Price et al., 1996). A “semantic gradient” in the Stroop effect (Klein, 1964), which manifests early in the process of learning to read (Schadler and Thissen, 1981), demonstrates that processing of words is obligatory even for beginning readers. Importantly, young children can perform the feature detection task accurately because they are not explicitly required to read the words, minimizing performance differences between subjects of different ages or reading abilities. Previous studies have demonstrated the utility of this task in avoiding performance confounds in comparisons of subjects of different reading abilities (Brunswick et al., 1999; Paulesu et al., 2001) or different ages (Turkeltaub et al., 2003). Furthermore, the control task, detection of ascenders within nonlexical stimuli (false font strings), controls as best as possible for brain processes required for task execution but not specifically engaged for covert reading per se, including visual and spatial processes, response selection, motor sequencing, and motor execution. Controlling for these domain general processes allowed examination of lexical processing differences between subjects without contamination from processes changing as a function of general nervous system maturation (Casey et al., 2000; Conel, 1939-1963; Huttenlocher and Dabholkar, 1997; Yakovlev and Lecours, 1967).

Subjects were trained on the feature detection task immediately prior to MRI sessions. To demonstrate their understanding of the task, subjects first identified words and false font strings with ascenders within a printed list of items. Subjects then completed a computer-administered practice run consisting of 10 words and 10 false font strings. No practice stimuli were repeated during fMRI data acquisition. Immediately following the imaging session, a forced choice recognition test was administered to assess level of covert reading during execution of the feature detection task. This test required subjects to recognize words presented during scanning from a list containing all presented words and an equal number of new words matched for length, frequency, and presence of ascenders and descenders. This posttest has previously confirmed that covert processing is related to reading ability (Turkeltaub et al., 2003) within the age range of subjects included in this study. Subjects were not informed of this test prior to scanning.

fMRI Data Acquisition

Series of whole-brain echo-planar images (EPI; TR = 4.2 s, TE = 40 ms, 64 × 64 matrix, 230 mm FOV, 46 axial slices, 3.6 mm cubic voxels) were acquired on a 1.5 Tesla Siemens Vision Magnetom scanner with a circularly polarized head coil. To minimize head motion and improve compliance, we trained children extensively on an MRI simulator prior to scanning, used foam pads to restrict head movement during scanning, and limited subjects’ time in the scanner to 25 min per session. Two MPRAGE 3D T1-weighted images were acquired for each subject. Each subject completed two 4.5 min imaging runs consisting of alternating epochs of crosshair fixation, feature detection on words, and feature detection on false font

strings (Figure 2). Each run began with a 16.8 s (4 TR) acclimation period to allow for longitudinal magnetization equilibration. Feature detection task epochs lasted 42 s, during which 10 stimuli were presented and 10 whole-brain EPI volumes were acquired. Crosshair fixation epochs, lasting 16.8 s, occurred between word epochs and false font string epochs. Thus, each imaging run proceeded as follows: Acclimation, Fixation, Word Task, Fixation, False Font String Task, fixation, Word Task, Fixation, False Font String Task, Fixation. Over two runs, 40 words and 40 false font string stimuli were presented. In total, 120 whole-brain EPI volumes were acquired, 40 per condition (words, false font strings, fixation).

fMRI Data Analysis

Data Processing. Imaging data were analyzed using MEDx (Sensor Systems, Sterling, VA). Each run from each subject underwent the following processing steps: head motion detection and correction (Automated Image Registration (AIR) 6-parameter rigid body realignment algorithm) (Woods et al., 1998a, 1998b), global intensity normalization, Gaussian spatial filtering (10.8 mm FWHM), and high-pass temporal filtering (Butterworth 243.5 s cutoff). Images were checked for head motion and artifact to ensure the quality of data. Subjects were excluded if they had greater than 0.7 mm peak-to-peak head motion in any dimension on either run after motion correction, or if the combined Z map received an artifact rating of 5 or greater on a 7-point scale, as assessed by two blinded experts.

Single Subject Analysis. Individual subject statistical maps were created by (1) performing a t test between word and false font string volumes for each run, (2) aligning each resulting Z map with either the subject’s own high-resolution structural volume or the SPM99 Talairach template using an AIR 12-parameter linear affine transformation, and (3) combining Z maps from both runs into an overall single-subject Z map ($Z = (Z_1 + Z_2)/\sqrt{2}$). A critical threshold of $p < 0.001$ (uncorrected) was applied to Ethan’s single-subject Z map to determine significant areas of activation.

Ethan versus Control Groups. To compare Ethan to controls, we spatially normalized all single-run word-minus-false font string mean difference images to the SPM99 Talairach template. Each subject’s single-run mean difference images were then averaged to create a single-subject difference image. These word-minus-false font string difference images were entered into two “Compare Groups” designs in the SPM tools in MEDx. These tests created Z maps of differences in brain activity between (1) Ethan and chronological age-matched controls, and (2) Ethan and reading age-matched controls (see Table 3). The critical threshold for these comparisons was $p < 0.0001$ for maxima with 25 contiguous voxels at $p < 0.001$ per cluster (two-tailed, uncorrected). Ethan’s high-resolution anatomical image was normalized to the SPM99 Talairach template, and functional data was fused to this volume for visualization and localization of the activity. Renderings presented in figures are maximum intensity projections with a penetration distance of 25 mm.

Region-of-Interest (ROI) Analysis. Because the above statistical maps represent the difference between a single subject and a group, we were concerned that significant results might reflect small variations in the location of activity in the control group rather than a true difference in local signal magnitude between Ethan and the control group. To this end, we performed a ROI analysis to compare hyperlexic and normal brain activity in areas known to be engaged by mature readers. The ROIs were defined by a group map generated from 15 healthy monolingual right-handed adult subjects (age 20–22, 8 female) while performing the same covert reading task (see Turkeltaub et al., 2003). Data processing was identical to that performed on the pediatric data, including spatial normalization to the Talairach template. Using a mixed-effects model, a paired t test was performed between word and false font images to generate a group Z map of covert reading activity in the adult group. ROIs were derived from the clusters of significant activity identified in this statistical contrast (peak $p < 0.0005$, with at least 25 voxels at $p < 0.005$; see Turkeltaub et al., 2003; Figure 4). Using the areas known to be involved in mature reading, we evaluated differences between our hyperlexic and our two normally reading groups. Mean word-versus-false font percent difference values were calculated for Ethan and each control subject within these ROIs. This confirmatory analysis allowed for interpretation of the voxel-wise statistical results with a degree of conservatism appropriate to single case studies.

Acknowledgments

This work was supported by the National Alliance for Autism Research, the National Institute of Child Health and Human Development (HD37890 and HD40095), the National Institute of Mental Health (MH65000), and by the General Clinical Research Center Program of the National Center for Research Resources (MO1-RR13297), National Institutes of Health. We wish to thank Meagan Lansdale, Sarah Baron, Lauren Penniman, Carol Montgomery, and Greg Wallace for contributing to data collection. We also thank Cathy Price for her advice on development of the false font and Tom Zeffiro for his comments on the manuscript. We also wish to thank Ethan and his family and the control subjects for their participation.

Received: June 5, 2003

Revised: October 14, 2003

Accepted: December 1, 2003

Published: January 7, 2004

References

- Aaron, P.G., Frantz, S.S., and Manges, A.R. (1990). Dissociation between comprehension and pronunciation in dyslexic and hyperlexic children. *Reading and Writing* 2, 243–264.
- Aram, D.M. (1997). Hyperlexia: reading without meaning in young children. *Top. Lang. Disord.* 17, 1–13.
- Bradley, L., and Bryant, P. (1983). Categorising sounds and learning to read—a causal connection. *Nature* 301, 419–421.
- Brunswick, N., McCrory, E., Price, C.J., Frith, C.D., and Frith, U. (1999). Explicit and implicit processing of words and pseudowords by adult developmental dyslexics: a search for Wernicke's Wortschatz? *Brain* 122, 1901–1917.
- Burd, L., and Kerbeshian, J. (1985). Hyperlexia and a variant of hypergraphia. *Percept. Mot. Skills* 60, 940–942.
- Burd, L., and Kerbeshian, J. (1989). Hyperlexia in Prader-Willi syndrome. *Lancet* 2, 983–984.
- Burd, L., Kerbeshian, J., and Fisher, W. (1985). Inquiry into the incidence of hyperlexia in a statewide population of children with pervasive developmental disorder. *Psychol. Rep.* 57, 236–238.
- Burd, L., Fisher, W., Knowlton, D., and Kerbeshian, J. (1986). Hyperlexia: a marker for improvement in children with pervasive developmental disorder? *J. Am. Acad. Child Adolesc. Psychiatry* 26, 407–412.
- Calvert, G.A. (2001). Crossmodal processing in the human brain: insights from functional neuroimaging studies. *Cereb. Cortex* 11, 1110–1123.
- Casey, B.J., Giedd, J.N., and Thomas, K.M. (2000). Structural and functional brain development and its relation to cognitive development. *Biol. Psychol.* 54, 241–257.
- Catts, H.W., Fey, M.E., Tomblin, J.B., and Zhang, X. (2002). A longitudinal investigation of reading outcomes in children with language impairments. *J. Speech Lang. Hear. Res.* 45, 1142–1157.
- Cobrinik, L. (1982). The performance of hyperlexic children on an “incomplete words” task. *Neuropsychologia* 20, 569–577.
- Cohen, M.J., Hall, J., and Riccio, C.A. (1997). Neuropsychological profiles of children diagnosed as specific language impaired with and without hyperlexia. *Arch. Clin. Neuropsychol.* 12, 223–229.
- Conel, J.L. (1939–1963). *The Postnatal Development of the Human Cerebral Cortex*, 6 volumes (Cambridge, MA: Harvard University Press).
- Eden, G.F., and Moats, L. (2002). The role of neuroscience in the remediation of students with dyslexia. *Nat. Neurosci.* 5 (Suppl.), 1080–1084.
- Eden, G.F., and Zeffiro, T.A. (1998). Neural systems affected in developmental dyslexia revealed by functional neuroimaging. *Neuron* 21, 279–282.
- Ehri, L.C. (1999). Phases of development in learning to read words. In *Reading Development and the Teaching of Reading: A Psychological Perspective*, J. Oakhill and R. Beard, eds. (Oxford: Blackwell Science Ltd.), pp. 79–108.
- Elliott, D.E., and Needleman, R.M. (1976). The syndrome of hyperlexia. *Brain Lang.* 3, 339–349.
- Fiez, J.A., and Petersen, S.E. (1998). Neuroimaging studies of word reading. *Proc. Natl. Acad. Sci. USA* 95, 914–921.
- Fiez, J.A., Balota, D.A., Raichle, M.E., and Petersen, S.E. (1999). Effects of lexicality, frequency, and spelling-to-sound consistency on the functional anatomy of reading. *Neuron* 24, 205–218.
- Fisher, W., Burd, L., and Kerbeshian, J. (1988). Markers for improvement in children with pervasive developmental disorders. *J. Ment. Defic. Res.* 32, 357–369.
- Flowers, L., Meyer, M., Lovato, J., Wood, F., and Felton, R. (2001). Does third grade discrepancy status predict the course of reading development. *Ann. Dyslexia* 51, 49–74.
- Frith, U. (1985). Beneath the surface of developmental dyslexia. In *Surface Dyslexia*, K.E. Patterson, J.C. Marshall, and M. Coltheart, eds. (London: Routledge and Kegan Paul), pp. 301–330.
- Frith, U., and Snowling, M. (1983). Reading for meaning and reading for sound in autistic and dyslexic children. *Br. J. Dev. Psych.* 1, 329–342.
- Gaillard, W.D., Pugliese, M., Grandin, C.B., Braniecki, S.H., Kondapaneni, P., Hunter, K., Xu, B., Petrella, J.R., Balsamo, L., and Basso, G. (2001). Cortical localization of reading in normal children: an fMRI language study. *Neurology* 57, 47–54.
- Gaillard, W.D., Balsamo, L.M., Ibrahim, Z., Sachs, B.C., and Xu, B. (2003). fMRI identifies regional specialization of neural networks for reading in young children. *Neurology* 60, 94–100.
- Georgiewa, P., Rzanny, R., Hopf, J.M., Knab, R., Glauche, V., Kaiser, W.A., and Blanz, B. (1999). fMRI during word processing in dyslexic and normal reading children. *Neuroreport* 10, 3459–3465.
- Georgiewa, P., Rzanny, R., Gaser, C., Gerhard, U.J., Vieweg, U., Freesmeyer, D., Mentzel, H.J., Kaiser, W.A., and Blanz, B. (2002). Phonological processing in dyslexic children: a study combining functional imaging and event related potentials. *Neurosci. Lett.* 318, 5–8.
- Glosser, G., Friedman, R., and Roeltgen, D.P. (1996). Clues to the cognitive organization of reading and writing from developmental hyperlexia. *Neuropsychology* 10, 168–175.
- Glosser, G., Grugan, P., and Friedman, R.B. (1997). Semantic memory impairment does not impact on phonological and orthographic processing in a case of developmental hyperlexia. *Brain Lang.* 56, 234–247.
- Goldberg, T.E. (1987). On hermetic reading abilities. *J. Autism Dev. Disord.* 17, 29–44.
- Goldberg, T.E., and Rothermel, R.D. (1984). Hyperlexic children reading. *Brain* 107, 759–785.
- Hagoort, P., Indefrey, P., Brown, C., Herzog, H., Steinmetz, H., and Seitz, R.J. (1999). The neural circuitry involved in the reading of German words and pseudowords: a PET study. *J. Cogn. Neurosci.* 11, 383–398.
- Healy, J.M. (1982). The enigma of hyperlexia. *Reading Res. Q.* 17, 319–338.
- Healy, J.M., Aram, D.M., Horwitz, S.J., and Kessler, J.W. (1982). A study of hyperlexia. *Brain Lang.* 17, 1–23.
- Høien, T., and Lundberg, I. (1988). Stages of word recognition in early reading development. *Scand. J. Educ. Res.* 32, 163–182.
- Huttenlocher, P.R., and Dabholkar, A.S. (1997). Regional differences in synaptogenesis in human cerebral cortex. *J. Comp. Neurol.* 387, 167–178.
- Huttenlocher, P.R., and Huttenlocher, J. (1973). A study of children with hyperlexia. *Neurology* 23, 1107–1116.
- Kanner, L. (1943). Autistic disturbances of affective contact. *Nervous Child* 2, 217–250.
- Kistner, J., Robbins, F., and Haskett, M. (1988). Assessment and skill remediation of hyperlexic children. *J. Autism Dev. Disord.* 18, 191–205.

- Klein, G.S. (1964). Semantic power measured through the interference of words with color-naming. *Am. J. Psychol.* 77, 576–588.
- Lindamood, C., and Lindamood, P. (1979). Lindamood Auditory Conceptualization (LAC) Test (Austin, TX: Pro-Ed).
- Lovaas, O.I., and Smith, T. (1989). A comprehensive behavioral theory of autistic children: paradigm for research and treatment. *J. Behav. Ther. Exp. Psychiatry* 20, 17–29.
- Lyon, G.R. (1995). Toward a definition of dyslexia. *Ann. Dyslexia* 45, 3–25.
- Mehegan, C.C., and Dreifuss, F.E. (1972). Hyperlexia. Exceptional reading ability in brain-damaged children. *Neurology* 22, 1105–1111.
- Nation, K. (1999). Reading skills in hyperlexia: a developmental perspective. *Psychol. Bull.* 125, 338–355.
- Patti, P.J., and Lupinetti, L. (1993). Brief report: implications of hyperlexia in an autistic savant. *J. Autism Dev. Disord.* 23, 397–405.
- Paulesu, E., McCrory, E., Fazio, F., Menoncello, L., Brunswick, N., Cappa, S.F., Cotelli, M., Cossu, G., Corte, F., Lorusso, M., et al. (2000). A cultural effect on brain function. *Nat. Neurosci.* 3, 91–96.
- Paulesu, E., Demonet, J.F., Fazio, F., McCrory, E., Chanoine, V., Brunswick, N., Cappa, S.F., Cossu, G., Habib, M., Frith, C.D., and Frith, U. (2001). Dyslexia: cultural diversity and biological unity. *Science* 291, 2165–2167.
- Poldrack, R.A., Wagner, A.D., Prull, M.W., Desmond, J.E., Glover, G.H., and Gabrieli, J.D. (1999). Functional specialization for semantic and phonological processing in the left inferior prefrontal cortex. *Neuroimage* 10, 15–35.
- Price, C. (1997). Functional Anatomy of Reading. In *Human Brain Function*, R. Frackowiak, C. Frith, R. Dolan, and J. Mazziotta, eds. (San Diego, CA: Academic Press), pp. 301–327.
- Price, C.J. (2000). The anatomy of language: contributions from functional neuroimaging. *J. Anat.* 197, 335–359.
- Price, C.J., Wise, R.J., and Frackowiak, R.S. (1996). Demonstrating the implicit processing of visually presented words and pseudowords. *Cereb. Cortex* 6, 62–70.
- Pugh, K.R., Shaywitz, B.A., Shaywitz, S.E., Constable, R.T., Skudlarski, P., Fulbright, R.K., Bronen, R.A., Shankweiler, D.P., Katz, L., Fletcher, J.M., and Gore, J.C. (1996a). Cerebral organization of component processes in reading. *Brain* 119, 1221–1238.
- Pugh, K.R., Shaywitz, B.A., Shaywitz, S.E., Constable, R.T., Skudlarski, P., Fulbright, R.K., Bronen, R.A., Shankweiler, D.P., Katz, L., Fletcher, J.M., and Gore, J.C. (1996b). Cerebral organization of component processes in reading. *Brain* 119, 1221–1238.
- Pugh, K.R., Mencl, W.E., Jenner, A.R., Katz, L., Frost, S.J., Lee, J.R., Shaywitz, S.E., and Shaywitz, B.A. (2001). Neurobiological studies of reading and reading disability. *J. Commun. Disord.* 34, 479–492.
- Raij, T., Uutela, K., and Hari, R. (2000). Audiovisual integration of letters in the human brain. *Neuron* 28, 617–625.
- Richman, L.C., and Wood, K.M. (2002). Learning disability subtypes: classification of high functioning hyperlexia. *Brain Lang.* 82, 10–21.
- Rumsey, J.M., Andreason, P., Zametkin, A.J., Aquino, T., King, A.C., Hamburger, S.D., Pikus, A., Rapoport, J.L., and Cohen, R.M. (1992). Failure to activate the left temporoparietal cortex in dyslexia. An oxygen 15 positron emission tomographic study. *Arch. Neurol.* 49, 527–534.
- Rumsey, J.M., Nace, K., Donohue, B., Wise, D., Maisog, J.M., and Andreason, P. (1997). A positron emission tomographic study of impaired word recognition and phonological processing in dyslexic men. *Arch. Neurol.* 54, 562–573.
- Schadler, M., and Thissen, D.M. (1981). The development of automatic word recognition and reading skill. *Mem. Cognit.* 9, 132–141.
- Schlaggar, B.L., Brown, T.T., Lugar, H.M., Visscher, K.M., Miezin, F.M., and Petersen, S.E. (2002). Functional neuroanatomical differences between adults and school-age children in the processing of single words. *Science* 296, 1476–1479.
- Seymour, H.K., and Evans, H.M. (1992). Beginning reading without semantics: a cognitive study of hyperlexia. *Cogn. Neuropsychol.* 9, 89–122.
- Shaywitz, S.E., Shaywitz, B.A., Pugh, K.R., Fulbright, R.K., Constable, R.T., Mencl, W.E., Shankweiler, D.P., Liberman, A.M., Skudlarski, P., Fletcher, J.M., et al. (1998). Functional disruption in the organization of the brain for reading in dyslexia. *Proc. Natl. Acad. Sci. USA* 95, 2636–2641.
- Shaywitz, B.A., Shaywitz, S.E., Pugh, K.R., Mencl, W.E., Fulbright, R.K., Skudlarski, P., Constable, R.T., Marchione, K.E., Fletcher, J.M., Lyon, G.R., and Gore, J.C. (2002). Disruption of posterior brain systems for reading in children with developmental dyslexia. *Biol. Psychiatry* 52, 101–110.
- Siegel, L.S. (1984). A longitudinal study of a hyperlexic child: hyperlexia as a language disorder. *Neuropsychologia* 22, 577–585.
- Silberberg, N., and Silberberg, M. (1967). Hyperlexia: specific word recognition skills in young children. *Except. Child.* 34, 41–42.
- Simos, P.G., Breier, J.I., Fletcher, J.M., Foorman, B.R., Bergman, E., Fishbeck, K., and Papanicolaou, A.C. (2000a). Brain activation profiles in dyslexic children during non-word reading: a magnetic source imaging study. *Neurosci. Lett.* 290, 61–65.
- Simos, P.G., Breier, J.I., Wheless, J.W., Maggio, W.W., Fletcher, J.M., Castillo, E.M., and Papanicolaou, A.C. (2000b). Brain mechanisms for reading: the role of the superior temporal gyrus in word and pseudoword naming. *Neuroreport* 11, 2443–2447.
- Simos, P.G., Breier, J.I., Fletcher, J.M., Foorman, B.R., Mouzaki, A., and Papanicolaou, A.C. (2001). Age-related changes in regional brain activation during phonological decoding and printed word recognition. *Dev. Neuropsychol.* 19, 191–210.
- Snowling, M. (1987). *Hyperlexia. Dyslexia: A Cognitive Developmental Perspective* (Oxford: Basil Blackwell).
- Sparks, R.L. (1995). Phonemic awareness in hyperlexic children. *Reading and Writing* 7, 217–235.
- Tanaka, K. (1997). Mechanisms of visual object recognition: monkey and human studies. *Curr. Opin. Neurobiol.* 7, 523–529.
- Temple, C.M. (1990). Auditory and reading comprehension in hyperlexia: semantic and syntactic skills. *Reading and Writing* 2, 297–306.
- Temple, E., Poldrack, R.A., Salidis, J., Deutsch, G.K., Tallal, P., Merzenich, M.M., and Gabrieli, J.D. (2001). Disrupted neural responses to phonological and orthographic processing in dyslexic children: an fMRI study. *Neuroreport* 12, 299–307.
- Tirosh, E., and Canby, J. (1993). Autism with hyperlexia: a distinct syndrome? *Am. J. Ment. Retard.* 98, 84–92.
- Treiman, R. (2000). The foundations of literacy. *Curr. Dir. Psychol. Sci.* 9, 89–92.
- Turkeltaub, P., Eden, G., Jones, K., and Zeffiro, T. (2002). Meta-analysis of the functional neuroanatomy of single-word reading: method and validation. *Neuroimage* 16, 765–780.
- Turkeltaub, P.E., Gareau, L., Flowers, D.L., Zeffiro, T.A., and Eden, G.F. (2003). Development of neural mechanisms for reading. *Nat. Neurosci.* 6, 767–773.
- Wagner, R.K., and Torgesen, J.K. (1987). The nature of phonological processing and its causal role in the acquisition of reading skills. *Psychol. Bull.* 101, 192–212.
- Wagner, R.K., Torgesen, J.K., Laughon, P., Simmons, K., and Rashotte, C.A. (1993). Development of young readers phonological processing abilities. *J. Educ. Psychol.* 85, 83–103.
- Wagner, R.K., Torgesen, J.K., Rashotte, C.A., Hecht, S.A., Barker, T.A., Burgess, S.R., Donahue, J., and Garon, T. (1997). Changing relations between phonological processing abilities and word-level reading as children develop from beginning to skilled readers: a 5-year longitudinal study. *Dev. Psychol.* 33, 468–479.
- Wechsler, D. (1991). *Wechsler Intelligence Scale for Children, Third Edition* (San Antonio, TX: The Psychological Corporation).
- Welsh, M.C., Pennington, B.F., and Rogers, S. (1987). Word recognition and comprehension skills in hyperlexic children. *Brain Lang.* 32, 76–96.
- Whitehouse, D., and Harris, J.C. (1984). Hyperlexia in infantile autism. *J. Autism Dev. Disord.* 14, 281–289.
- Woods, R.P., Grafton, S.T., Holmes, C.J., Cherry, S.R., and Mazziotta, J.C. (1998a). Automated image registration: I. General methods

and intrasubject, intramodality validation. *J. Comput. Assist. Tomogr.* 22, 139–152.

Woods, R.P., Grafton, S.T., Watson, J.D., Sicotte, N.L., and Mazziotta, J.C. (1998b). Automated image registration: II. Intersubject validation of linear and nonlinear models. *J. Comput. Assist. Tomogr.* 22, 153–165.

Yakovlev, P.I., and Lecours, A.R. (1967). The myelogenetic cycles of regional maturation of the brain. In *Regional Development of the Brain in Early Life*, A. Minkowski, ed. (Philadelphia, PA: Davis Co.), pp. 3–70.

Yeargin-Allsopp, M., Rice, C., Karapurkar, T., Doernberg, N., Boyle, C., and Murphy, C. (2003). Prevalence of autism in a US metropolitan area. *JAMA* 289, 49–55.