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Where and *what* visuospatial processing in adolescents with congenital hypothyroidism

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Abstract

Visuospatial processing is accomplished in distinct neuroanatomic pathways. One such pathway, known as the *where* pathway, involves a dorsal route through magnocellular thalamic cells to occipital and parietal cortices and conveys location and motion information. A second pathway, known as the *what* pathway, involves a ventral route through parvocellular thalamic cells to occipital and temporal cortices and conveys color and form information. The *where* pathway is thought to be responsible for processing spatial relationships while the *what* pathway is responsible for object identification. Children with early-treated congenital hypothyroidism (CH) who exhibit selective visuospatial deficits may provide a good model to study the differential development of these pathways. Because children with CH lacked thyroid hormone at a time when needed by developing brain regions such as the parietal cortex, these children may be affected to a greater degree on tasks tapping *where* but not *what* pathway processing. We tested this hypothesis via retrospective analysis of their performance on 6 spatial tasks. Compared were 49 adolescents with CH and 49 matched control participants. On the basis of confirmatory factor analysis, tasks were assigned to either *where* or *what* pathway groupings. A repeated measures ANOVA showed the CH group was impaired relative to a normal comparison group only on *where* pathway tasks. Regression analyses indicated that severity of early hypothyroidism was the strongest predictor of *where* pathway processing but had no effect on *what* pathway tasks. It is concluded that thyroid hormone is required during late gestation and early life for the normal development of the *where* aspects of visuospatial processing. (*JINS*, 2001, *7*, 556–562.)

Keywords: Visuospatial ability, Visual cortex, Neuroanatomic pathways, Congenital hypothyroidism

INTRODUCTION

The existence of segregated neuroanatomic pathways for visuospatial processing was first described almost two decades ago in studies of primates (Mishkin et al., 1983) and humans with circumscribed brain lesions from stroke or other injury (De Renzi, 1982; Goodale & Milner, 1992; Wilson et al., 1997). Such studies demonstrated that information pertaining to object location and motion is processed primarily via a dorsal route through the posterior parietal lobe, whereas information about object identification is processed via a ventral route through the striate cortex to the inferior temporal cortex (Hubel & Livingstone, 1987). For example, Ungerleider and Mishkin (1982) showed that the performance of monkeys on a landmark discrimination task assessing spatial relations (e.g., choosing the covered food well closer to the tall cylinder) was disrupted following posterior parietal cortex lesions, whereas performance on a delayed nonmatching-to-sample task assessing object recognition was unaffected; the opposite effects occurred from inferotemporal cortex lesions. More recently, PET (Haxby et al., 1994; Kosslyn et al., 1990; McIntosh et al., 1994) and fMRI studies (Ungerleider, 1995) have confirmed the existence of these pathways in normal adult humans who use a dorsal route for location information and a ventral route for object identification (Ungerleider & Mishkin, 1982).

The animal literature additionally reveals visuospatial information is originally segregated in retinal parasol and midget cells, which then project spatial or visual information to magnocellular (M) or parvocellular (P) cells in the lateral geniculate nucleus (LGN) of the thalamus. Because

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of the unique physiological properties of M and P cells, these each convey different kinds of information and the two neuroanatomic pathways have come to be known as the M and P pathways. M cells, which have a much larger receptive field than P cells (de Monsasterio & Gouras, 1975; Hubel & Livingstone, 1987), are more sensitive to change and low contrast frequencies (Derrington & Lennie, 1984), whereas P cells being smaller are more sensitive to high spatial contrasts (Merigan & Eskin, 1986). Also, M cells have faster latencies than P cells, whereas P cells are better able to sustain a response (Schiller, 1998; Schiller & Malpeli, 1978). This segregation of activities also continues past the LGN to different layers of the striate cortex and beyond, with a dorsal occipital–parietal path for direction, motion, and velocity information (Desimone & Ungerleider, 1989; Maunsell & Newsome, 1987) and a ventral occipitotemporal path for color, texture and shape information (Sereno, et al., 1995). Furthermore, there is cross-talk between pathways (Merigan & Maunsell, 1993) and feedback from other structures such as the frontal lobes (Ungerleider, 1995).

M and P cells of the LGN also differ in their rates of development (Hickey, 1977), as do the M and P pathways themselves with M-pathway development preceding P (Distler et al, 1996). In human infants, the ability to track stimuli by detecting motion and coarse visual detail (M-pathway activities) appears as early as 2 months of age (Columbo, 1995; Johnson et al., 1998; Norcia et al., 1990), in contrast to object recognition (P-pathway activities) that appears somewhat later at 3 months of age (Richards, 1997; Rose, 1983). Less is known about the development of these pathways at a higher more cognitive level or about abnormal pathway development in children with selective visuospatial deficits. Recent studies of children with adrenoleukodystrophies (E. Shapiro, personal communication, January 1996), extremely low birthweight or prematurity (A. Downey & V. Frisk, personal communication, April, 1999), and Turner syndrome (Buchanan et al., 1998; Rovet & Buchanan, 1999) suggest that M-pathway disruptions may be contributing to their specific deficits.

To identify endocrinologic factors associated M- and P-pathway development, we conducted an analysis of *where* versus *what* visuospatial abilities in children with early-treated congenital hypothyroidism (CH), who were detected by newborn screening and treated very early in life. Although CH was once a leading cause of mental retardation, newborn screening and immediate treatment have significantly reduced the cognitive deficits found in affected children. However even with early treatment, children with CH still show subtle persisting neuromotor (Fuggle et al., 1991) and neurocognitive deficits (Derksen-Lubsen & Verkerk, 1996), which contribute to early language delays (Gottschalk et al., 1994) and later visuospatial, memory, and attention deficits (Kooistra et al., 1996; Rovet & Alvarez, 1996; Rovet & Ehrlich, 1995; Rovet et al., 1992). Because their visuospatial deficit varies across tasks (Rovet, 1999a, 1999b), these children may provide a reasonable model to study the differential development of visuospatial processing pathways.

The visuospatial deficits of children with CH reflect their lack of thyroid hormone prior to and at the time of birth (Rovet et al., 1992). From studies of animals, it is known that thyroid hormone is essential for a number of major neurobiological processes (for reviews, see Bernal & Nunez, 1995; Porterfield & Hendrich, 1993) including neurogenesis (Nicholson & Altman, 1972), axon and dendrite formation (Legrand, 1984), and myelination (Rosman et al., 1972). Typically affected by an early lack of thyroid hormone are the cerebellum, hippocampus, and caudate, as well as parietal cortex and thalamus belonging to the M pathway (Bernal & Nunez, 1995). Thyroid hormone functions by regulating genes (Binder et al., 1985; Farsetti et al., 1992; see also Porterfield & Stein, 1994), the transcriptional products of which are the essential proteins that underlie the above neurobiological events (Bernal & Nunez, 1995). Gene regulation is accomplished by the formation of a nuclear receptor complex between thyroid hormone and a thyroid hormone receptor (Brent, 1994). This complex in turn activates (or deactivates) specific genes (de Viljder et al., 1997). Studies by Bradley et al. (1992) have shown that in the rat, thyroid hormone receptors have distinct patterns of spatiotemporal expression during neurodevelopment with more dense distribution in posterior than anterior cortical regions and importantly for this paper, more for M than P LGN cells (Bradley et al., 1989). This observation prompted our hypothesis that the visuospatial impairment of children with CH may be selective for tasks that draw more heavily on dorsal stream or *where* processes than ventral stream or *what* processes.

To test this hypothesis, we conducted a retrospective analysis of the visuospatial task performance in adolescents diagnosed with CH *via* newborn screening. These individuals were long-time participants in a prospective follow-up study that included an extensive neuropsychological evaluation at adolescence. As part of this assessment, they received multiple visuospatial tasks assessing both spatial orientation/location and object identification components. For present purposes, tasks were grouped according to their *where* or *what* pathway requirements. The major questions were, (1) Do groups differ selectively on *where* or *what* pathway tasks? and (2) Are effects on pathway performance in the CH group related to severity of the thyroid hormone deficiency?

METHODS

Research Participants

Forty-nine participants with CH (13 boys) were studied at a mean age of 13.9 ± 1.3 years (range = 12.0–17.4 years). These children, who were born between 1976 and 1982, represented the majority of the oldest remaining children in a large cohort identified originally by one or both of two neonatal screening programs in Ontario (see Rovet, 1999b,

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for a description). Of the 49 participants, 13 lacked an entire thyroid gland, 23 had an ectopic gland, and 13 had a normally located but dysfunctional gland. Fifty percent of the group demonstrated delayed skeletal maturity at diagnosis (bone age less than 37 weeks gestation) suggestive of intrauterine hypothyroidism. Their mean thyroxine (T4) level at diagnosis was 77.1 ± 57.2 mmol/L (normal range = 100 to 200 mmol/L), with 34% of the children having a value below 40 mmol/L. The children were initially treated at 16.4 ± 22 days of age with a mean starting dose of 9.3 ± 5 mg/kg levothyroxine. At time of testing, their mean free T4 level was 16.2 ± 3.0 pmol/L (normal range = 10 to 23 pmol/L), total T4 level was 113.8 ± 31 mmol/L (normal range = 65 to 165 nmol/L), and TSH was 6.7 ± 9.l1 mU/L (normal range = 0.5 to 5.0 mU/L), with 33% of the group having a TSH value above normal.

Control participants were 49 healthy adolescents (13 boys) matched for gender and age (within 6 months) with a child with CH. They were drawn from a large control pool assessed with the same set of tests as part of an ancillary study. Their mean age was 14.0 ± 1.4 years (range = 11.7 to 17.3 years).

Tests and Measures

As part of a comprehensive neuropsychological evaluation, all participants received six measures of visuospatial processing described in Table 1. The overall test battery was administered in one of four set orders, which were randomly assigned to different subjects. Each test order contained four blocks provided before and after the midmorning snack and before and after the midafternoon break. Each block contained an equivalent number of tests of comparable difficulty, interest value, and attentional requirements. The visuospatial tasks were administered in each of the four blocks, generally toward the end of each. A lunch break and two 15-min snack breaks were provided.

For each child with CH, the following information was recorded from the medical chart: etiology of hypothyroidism, bone age at diagnosis, age at treatment onset, starting dose level, and age at normalization of hypothyroidism (see Rovet et al., 1992). Also recorded were the child's thyroid hormone levels at time of testing. An index of initial disease severity was derived by computing the average of the child's skeletal maturity converted to a *z* score, T4 level at diagnosis (*z* score), and a weighted score for the child's etiological group based on the group's average T4 level at diagnosis.

Data Analysis

Groups were compared across spatial tests using MANOVA. A principal components factor analysis with a varimax rotation was conducted (on control data) to identify relevant visuospatial factors. For all subjects, the averaged standardized scores of the tests comprising each factor were com-

Table 1. Description of visuospatial tasks

Measure	Requirements
Judgement of Line Orientation (Benton et al., 1978)	This task requires the identification of lines matching a target within an array of differently oriented lines. The test is scored according to established norms.
Block Design (Wechsler, 1974)	This timed task requires participants to use patterned cubes to construct a series of block arrays that conform to a model. Arrays become progressively more complex with successive trials. The test is scored according to established norms.
Memory for Human Faces (Denman, 1984)	This task presents a card containing 16 black and white faces for a brief period. After a 1.5-min delay, participants are shown an array of 48 faces and must identify the original 16 in it. The test is scored according to established norms.
Picture Completion (Wechsler, 1974)	In this task, participants view a series of successively presented cards, each containing a line drawing of a familiar object in which a feature is missing. The task is to identify the missing feature by pointing to it. The test is scored according to established norms.
Mental Rotation (Vandenburg & Kuse, 1978)	This is a paper-and-pencil test presenting a target shape and alternative shapes in different orientations. The task is to identify the shapes matching the target. The test is scored according to percent of items correctly identified.
Object Identification (Kimura et al., 1981)	This is a visual search task presented on a board containing 86 line drawings of common objects. Participants view the board for 120 s, following which they are given in succession 20 cards showing one of the original objects. Their task is to locate the target items on the board as quickly as possible. Time to identify the correct object is scored.

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Table 2. Comparison of groups on the six visuospatial tasks

Task	CH		Control		*p* level
	M	*SD*	*M*	*SD*	
Line Orientation[a]	38.3	27.2	49.6	26.2	.05
Block Design[b]	11.1	2.8	12.7	2.3	.01
Memory Human Faces[b]	10.8	3.1	9.8	3.9	n.s.
Mental Rotation[c]	15.2	9.1	20.7	3.9	.01
Picture Completion[b]	9.7	2.7	11.6	2.9	.01
Object Identification[d]	4.68	1.9	4.64	1.9	n.s.

Note. Scored as [a]percentiles, [b]scaled scores ($M = 10$; $SD = 3$), [c]raw score (percent correct), [d]mean RT.

puted and served as pathway scores. These data were analyzed using a repeated measures ANOVA with group as the between-subjects factor and pathway as the within-subjects factor. For the CH group, multiple regression analysis was used to examine the relation between indices of early hypothyroidism severity, current thyroid hormone levels, and pathway scores.

RESULTS

The MANOVA was significant [$F(6,84) = 2.92$, $p < .01$] and reflected the poorer overall performance of children with CH. Univariate analyses revealed the groups differed significantly at the $p < .01$ level on Picture Completion, Mental Rotation, and Block Design [$F(1,89) = 9.13$, 8.09, and 7.34 respectively] and at the $p < .05$ level on the Judgment of Line Orientation task [$F(1,89) = 4.54$]. In each case, the CH group scored lower than the control group (see Table 2). The groups did not differ on the Memory for Human Faces or Object Identification.

A principal components factor analysis showed three significant factors with Eigenvalues above 1.0 (see Table 3). The first factor, which accounted for 44% of the variance and included Block Design, Picture Completion, Benton Line Orientation, and Mental Rotation tests, appeared to reflect *where* or M-pathway processing. The second factor, which accounted for 17.4% of the variance, included Memory for Human Faces while the third factor, which accounted for 16.2% of the variance, included Object Identification. Because the latter two factors reflected different aspects of *what* processing that are known to implicate the ventral stream with different projections into the inferotemporal lobe (Clark et al., 1996), we combined these results to form a single *what* pathway factor. Individual *where* and *what* pathway composite scores were obtained for each participant. A repeated measures ANOVA indicated a significant group × pathway interaction [$F(1,95) = 14.24$, $p < .001$], with no main effects of group or pathway. *Post-hoc* analyses revealed the interaction was due to the significantly poorer performance of children with CH on *where* [$t(97) = 11.84$, $p < .001$], but not *what* pathway tasks [$t(97) = .65$] (see Fig. 1).

Table 3. Results of factor analysis and individual factor loadings[a]

Where		*What*	
Task	Factor Loading	Task	Factor Loading
Line Orient	.899	Memory for Faces[1]	.921
Mental Rotation	.841	Object Identification[2]	.975
Picture Completion	.756		
Block Design	.714		

Note. [a]Based on normal comparison group; [1]loads on Factor 2; [2]loads on Factor 3.

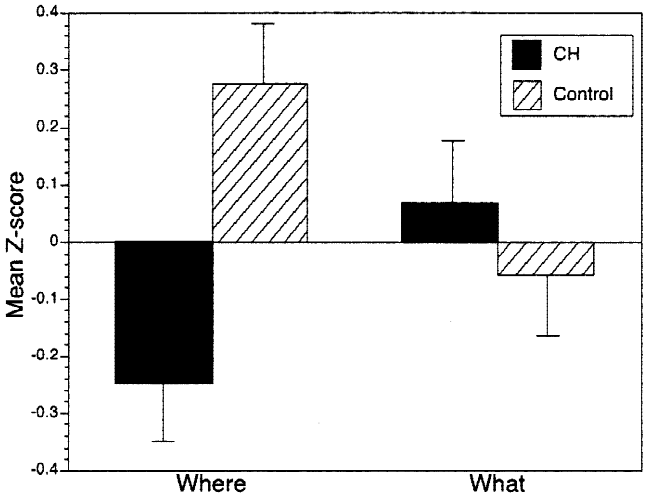

Fig. 1. Performance on *where* and *what* pathway processing in CH and control groups. Results are presented as averaged *z* scores across tasks within factors.

To assess the relative impact of the various disease and treatment indices on performance in the two pathways, hierarchical multiple regression analyses were computed entering initial severity, treatment age, age at normalization, and T4 at time of testing as predictors. The results indicated a significant multiple correlation for *where* [$F(1,28) = 7.43$, $p < .01$, $R^2 = .210$] processing. The *where* effect was accounted for mainly by initial severity of hypothyroidism [$t(47) = 2.5$, $p < .01$, $R^2 = .241$] with the other three predictors contributing minimally ($R^2 = 0$, .014, .002, respectively). For *what* processing, the multiple regression was not significant with the four predictors accounting collectively for only 11.7% of the variance. It is interesting to note that the strongest predictor of *what* processing was T4 level at time of testing, which accounted for 8.3% of the variance compared to 0.1%, 3.2%, and 0.1% for initial severity, treatment age, and time to normalization.

DISCUSSION

Our initial hypothesis was prompted by the literature showing both a divergence of visuospatial pathways and a dif-

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ferential distribution of thyroid hormone receptors in cortical and subcortical neuroanatomic structures of one of the putative visuospatial pathways. We proposed that CH children, who lack thyroid hormone prior to and shortly after birth, would show selective impairments in *where* or M-pathway development but would have spared *what* or P-pathway development. Our present findings were derived from retrospective analysis of the visuospatial performance data of early-treated CH adolescents and a matched comparison group, all of whom were tested with multiple spatial tasks. The results revealed the CH group performed significantly poorer than control participants on four of the six tasks representing aspects of *where* processing. The groups did not differ on two tasks thought to invoke the *what* pathway, namely Object Identification and Memory for Human Faces. Factor analysis confirmed these processing distinctions with one factor representing the tasks presumed to assess *where* pathway processes and the other two factors assessing different aspects of *what* pathway processing. When we combined the latter two factors and compared averaged scores within the two main factors, the results showed an interaction reflecting a significant group difference on the *where* but not the *what* pathway, with the CH group performing more poorly on *where*.

Our second hypothesis dealt with whether *where* task impairment reflected the timing and severity of thyroid hormone deficiency. Multiple regression analyses showed that severity of initial hypothyroidism was the single strongest predictor of poor *where* pathway performance but had no effect on *what* pathway performance. This suggests that a lack of thyroid hormone during late gestation and early life (as measured by the severity index) may have compromised *where* pathway performance in brain regions belonging to the dorsal stream or M-pathway of visuospatial processing. These findings are thought to provide additional support for the notion of distinct segregated visuospatial pathways in children and the differential susceptibility of these pathways to neonatal thyroid hormone insufficiency. While these findings concur with animal studies showing brain areas contributing to the *where* pathway (namely, parietal cortex and magno cells of the LGN) have a substantial density of thyroid hormone receptors, the need for neuroimaging studies of children with CH is clearly indicated in order to determine whether underlying structures do develop abnormally.

Although our findings suggest no effect of early thyroid hormone deficiency on *what* pathway development, this may reflect the relatively restricted time period when our sample was lacking thyroid hormone (i.e., from the latter part of gestation in about half the cases to the 1st month of early life). It is possible that the *what* pathway is also sensitive to a lack of hormone, but the critical time window occurs after the time of treatment for children in our sample. Based on developmental findings of infants, P-pathway development lags behind M-pathway development. If this is the case for *what* and *where* processing distinctions, one would expect that *what* task performance would correlate with indices of later but not earlier hypothyroidism. In particular, we expected that performance on these tasks would correlate most strongly with the index of postnatal hypothyroid duration. Indeed, supplementary univariate correlations showed that an index of *what* pathway performance did correlate with time until thyroid hormone levels normalized (approximately 3 months of age; Rovet et al., 1992) [$r(47) = -.297$, $p < .05$], but not with indices of earlier thyroid hormone deficiency. While an alternative explanation for the lack of effects on *what* pathway performance may reflect the different levels of difficulty of tasks belonging to each of the pathways, additional analyses showed that IQ correlated significantly with all tasks comprising each factor. Furthermore, when the ANOVA was repeated with IQ as a covariate, effects were strengthened for the *where* factor and remained nonsignificant for the *what* factor. Thus, the effects reported here cannot be attributed to task difficulty.

This study aimed to integrate neuroscience theory of visual processing with the role of thyroid hormone in early brain development and in so doing provide clinical insights on the specific sequelae of the brief period of thyroid hormone insufficiency. However, there are several limitations including a retrospective approach and inferences about brain structures from test performance. It is recommended that rather than use existing clinical tasks, *what* and *where* processes should be studied directly using behavioral paradigms that dissociate the pathways (e.g., landmark *vs.* sample matching tasks), as we have done on another population of children (Buchanan et al., 1998). In addition, neurophysiological and neuroimaging techniques during visuospatial processing may serve to clarify more precisely those pathways that are activated or disrupted in this population of children. This information will be invaluable in determining how exactly thyroid hormone affects early human brain development, about which little is presently known.

From a clinical standpoint, the present results signify that children with more severe CH at time of diagnosis are more likely to have impairments on *where* pathway tasks, which have implications for school functioning. We have reported elsewhere (Rovet & Ehrlich, 2000) that these same children exhibit nonspecific math problems in the early grades but catch up later in math. However, they continue to perform more poorly than classmates in complex school subjects such as science and social studies that make considerable demands on visuospatial processing (e.g., reading graphs and maps, applying chemical symbols, viewing biological structures).

In conclusion, present findings from our cohort of adolescents with CH who underwent a brief postnatal period of hypothyroidism showed permanent and selective effects on visuospatial processing. Primarily affected were their abilities to process spatial location and relational information, which are known to depend on the dorsal occipitoparietal or M pathway of the brain. Furthermore, processing in this domain was predicted by severity of early hypothyroidism. While *what* pathway processing was not affected in these children, the vulnerable period may be beyond when they

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were thyroid hormone deficient and, indeed, children who took longer to establish normal thyroid hormone levels did perform more poorly in this domain. It is suggested that future studies consider examining structural and functional development of these pathways more directly using neuroimaging techniques.

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REFERENCES

Benton, A.L., Varny, N.R., & Hamsher, K. (1978). Visuospatial judgement. A clinical test. *Archives of Neurology*, *35*, 364–367.

Bernal, J. & Nunez, J. (1995). Thyroid hormones and brain development. *European Journal of Endocrinology*, *133*, 390–398.

Binder, L.I., Frankfurter, A., & Rebhun, L.I. (1985). The distribution of *tau* in the mammalian central nervous system. *Journal of Cell Biology*, *101*, 1371–1378.

Bradley, D.J., Towle, H.C., & Young, W., III. (1992). Spatial and temporal expression of alpha and beta thyroid hormone receptor mRNAs, including the beta2 subtype, in the developing mammalian nervous system. *Journal of Neuroscience*, *12*, 2288–2302.

Bradley, D., Young, W., & Weinberger, C. (1989). Differential expression α and β thyroid hormone receptor genes in rat brain and pituitary. *Neurobiology*, *86*, 7250–7254.

Brent, G.A. (1994). The molecular basis of thyroid hormone action. *New England Journal Medicine*, *331*, 847–853.

Buchanan, L., Pavolovic, J., & Rovet, J. (1998). A reexamination of the visuospatial deficit in Turner Syndrome: Contributions of working memory. *Developmental Neuropsychology*, *14*, 341–368.

Clark, V.P., Keil, K., Maisog, J.M., Courtney, S., Underleider, L.G., Haxby, J.V. (1996). Functional magnetic resonance imaging of human visual cortex during face matching: A comparison with positron emission tomography. *Neuroimage*, *4*, 1–15.

Columbo, J. (1995). On the neural mechanisms underlying developmental and individual differences in visual fixation in infancy: Two hypotheses. *Developmental Review*, *15*, 97–135.

De Monsaterio, F.M. & Gouras, P. (1975). Functional properties of ganglion cells of the rhesus monkey retina. *Journal of Physiology*, *251*, 167–195.

Denman, S.B. (1984). *Denman Neuropsychology Memory Scale*. Charleston, SC: Denman.

DeRenzi, E. (1982). *Disorders of space exploration and cognition*. New York: Wiley.

Derksen-Lubsen, G. & Verkerk, P.H. (1996). Neuropsychologic development in early treated congenital hypothyroidism: Analysis of literature data. *Pediatric Research*, *39*, 561–566.

Derrington, A.M. & Lennie, P. (1984). Spatial and temporal contrast sensitivities of neurones in lateral geniculate nucleus of macaque. *Journal of Physiology*, *357*, 219–240.

Desimone, R. & Ungerleider, L.G. (1989). Neural mechanisms of visual processing in monkeys. In F. Boller & J. Grafman (Eds.), *Handbook of neuropsychology* (Vol. 2, pp. 267–299). Amsterdam: Elsevier.

de Viljder, J.J.M., Ris-Stalpers, C., & Vulsma, T. (1997). Inborn errors of thyroid hormone biosynthesis. *Experimental and Clinical Endocrinology and Diabetes*, *105* (Suppl. 4), 32–37.

Distler, C., Bachevalier, J., Kennedy, C., Mishkin, M., & Ungerleider, L.G. (1996). Functional development of the corticocortical pathway for motion analysis in the macaque monkey: A 14C-2-deoxyglucose study. *Cerebral Cortex*, *6*, 184–195.

Farsetti, A., Desvergne, B., Hallenbeck, P., Robbins, J., & Nikodem, V.M. (1992). Characterization of myelin basic protein thyroid hormone response element and its function in the context of native and heterologus promoter. *Journal of Biological Chemistry*, *267*, 15784–15788.

Fuggle, P.W., Grant, D.B., Smith, I., & Murphy, G. (1991). Intelligence, motor skills and behaviour at 5 years in early-treated congenital hypothyroidism. *European Journal of Pediatrics*, *150*, 570–574.

Goodale, M.A. & Milner, A.D. (1992). Separate visual pathways for perception and action. *Trends in Neurosciences*, *15*, 20–25.

Gottschalk, B., Richman, R., & Lewandowski, L. (1994). Subtle speech and motor deficits of children with congenital hypothyroidism treated early. *Developmental Medicine and Child Neurology*, *36*, 216–220.

Haxby, J.V., Horwitz, B., Underleider, L.G., Maisog, J.M., Pietrini, P., & Grady, C.L. (1994). The functional organization of human extrastriate cortex: A PET-rCBF study of selective attention to faces and locations. *Journal of Neuroscience*, *14*, 6336–6353.

Hickey, T.H. (1977). Postnatal development of the human lateral geniculate nucleus: Relationship to a critical period for the visual system. *Science*, *198*, 836–838.

Hubel, D.H. & Livingstone, M.S. (1987). Segregation of form, color and stereopsis in primate area 18. *Journal of Neuroscience*, *7*, 3378–3415.

Johnson, M.H. (1995). The development of visual attention: A cognitive neuroscience perspective. In M.S. Gazzaniga (Ed.), *The cognitive neurosciences* (pp. 735–747). Cambridge MA: MIT Press.

Johnson, M.H., Gilmore, R.O., & Csibra, G. (1998). Toward a computational model of the development of saccade planning. In J.E. Richards (Ed.), *Cognitive neuroscience of attention: A developmental perspective* (pp.103–130). Mahwah NJ: Erlbaum.

Kimura, D., Barnett, H.J.M., & Burnhart, G. (1981). The psychological test pattern and progressive supranuclear palsey. *Neuropsychologia*, *19*, 301–306.

Kooistra, L., van der Meere, J.J., Vulsma, T., & Kalverboer, A.F. (1996). Sustained attention problems in children with early treated congenital hypothyroidism. *Acta Paediatrica*, *85*, 425–429.

Kosslyn, S.M., Flynn, R.A., Amsterdam, J.B., & Wang, G. (1990). Components of high-level vision: A cognitive neuroscience analysis and accounts of neurological syndromes. *Cognition*, *34*, 203–277.

Legrand, J. (1984). Effects of thyroid hormones on central nervous system development. In J. Yanat (Ed.), *Neurobehavioural Teratology* (pp. 331–363). Amsterdam: Elsevier.

Maunsell, J.H. & Newsome, W.T. (1987). Visual processing in monkey extrastriate cortex. *Annual Review of Neuroscience*, *10*, 363–401.

McIntosh, A.R., Grady, C.L., Ungerleider, L.G., Haxby, J.V., Rapoport, S.I., & Horwitz, B. (1994). Network analysis of cortical visual pathways mapped with PET. *Journal of Neuroscience*, *14*, 656–666.

Merigan, W.H. & Eskin, T.A. (1986). Spatio-temporal vision of macaques with severe loss of Pb retinal gangion cells. *Vision Research*, *26*, 1751–1761.

Merigan, W.H. & Maunsell, J.H.R. (1993). How parallel are the primate visual pathways? *Annual Review of Neuroscience*, *16*, 369–402.

Mishkin, M., Ungerleider, L.G. & Macko, K.A. (1983). Object vision and spatial vision: Two cortical pathways. *Trends in Neuroscience*, 414–417.

Nicholson, J.L. & Altman, J. (1972). Thyroid and developing cerebellum. *Brain Research*, *44*, 13–23

Norcia, A.M., Tyler, C.W., & Hamer, R.D. (1990). Development of contrast sensitivity in the human infant. *Vision Research*, *30*, 1475–1486.

Porterfield, S.P. & Hendrich, C.E. (1993). The role of thyroid hormones in prenatal and neonatal neurological development—Current perspectives. *Endocrine Review*, *14*, 94–106.

Porterfield, S.P. & Stein, S.A. (1994). Thyroid hormones and neurological development: Update. *Endocrine Review*, *25*, 357–363.

Richards, J.E. (1997). Effects of attention on infants' preference for briefly exposed visual stimuli in the paired-comparison recognition-memory paradigm. *Developmental Psychology*, *33*, 22–31.

Richards, J.E. & Hunter, S.K. (1998). Attention and eye movements in young infants: Neural control and development. In J.E. Richards (Ed.), *Cognitive neuroscience of attention* (pp. 131–162). Mahwah, NJ: Erlbaum.

Rose, S.A. (1983). Differential rates of visual information processing in full-term and preterm infants. *Child Development*, *54*, 1189–1198.

Rosman, N., Malone, M., Helfenstein, M., & Kraft, E. (1972) The effect of thyroid deficiency on myelination of the brain. *Neurology*, *22*, 99–106.

Rovet, J.F. (1999a). Congenital hypothyroidism: Long-term outcome. *Thyroid*, *9*, 741–748.

Rovet, J.F. (1999b). Long-term neuropsychological sequelae of early-treated congenital hypothyroidism. Effects in adolescence. *Acta Paediatrica*, *88*, 88–95.

Rovet, J. & Alvarez, M. (1996). Attention and thyroid hormone in school-age children with congenital hypothyroidism. *Journal of Child Psychology and Psychiatry*, *3*, 579–585.

Rovet, J. & Buchanan, L. (1999). Turner Syndrome. A cognitive neuroscience approach. In H. Tager-Flusberg (Ed.), *Neurodevelopmental disorders: Contributions to a new perspective from the cognitive neurosciences* (pp. 223–250). Cambridge, MA: MIT Press.

Rovet, J.F., & Ehrlich, R.M. (1995). Long-term effects of L-thyroxine therapy for congenital hypothyroidism. *Journal of Pediatrics*, *126*, 380–386.

Rovet, J.F., & Ehrlich, R.M. (2000). Psychoeducational outcome in children with early-treated congenital hypothyroidism. *Pediatrics*, *105*, 515–522.

Rovet, J., Ehrlich, R., & Sorbara D. (1992). Neurodevelopment in infants and preschool children with congenital hypothyroidism. Etiological and treatment factors affecting outcome. *Journal of Pediatric Psychology*, *17*, 187–213.

Schiller, P.H. (1998). The neural control of visually guided eye movements. In J.E. Richards (Ed.), *Cognitive neuroscience of attention* (pp. 3–50). Mahwah, NJ: Erlbaum.

Schiller, P.H. & Malpeli, J.G. (1978). Functional specificity of lateral geniculate nucleus laminae of the rhesus monkey. *Journal of Neurophysiology*, *41*, 788–797.

Sereno, M.E., Dale, A.M., Reppas, J.B., Kwong, K.K., Belliveau, J.W., Brady, T.J., Rosen, B.R., & Tootell, R.B. (1995). Borders of multiple visual areas in humans revealed by functional magnetic resonance imaging. *Science*, *268*, 889–893.

Ungerleider, L.G. (1995). Functional brain imaging studies of cortical mechanisms for memory. *Science*, *270*, 769–775.

Ungerleider, L.G. & Mishkin, M. (1982). Two cortical visual systems. In D.J. Ingle, M.A. Goodale, & R.J.W. Mansfield (Eds.), *Analysis of visual behavior* (pp. 549–586). Cambridge MA: MIT Press.

Vandenberg, S.G. & Kuse, A.R. (1978) Mental rotations: A group test of 3-dimensional spatial visualization. *Perceptual Motor Skills*, *47*, 599–604.

Wechsler, D. (1974). *Wechsler Intelligence Scale for Children–Revised*. New York: The Psychological Corporation.

Wilson, B.A., Clare, L., Young, A.W., & Hodges, J.R. (1997). Knowing where and knowing what: A double dissociation. *Cortex*, *33*, 529–541.