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Attention problems in adolescents with congenital hypothyroidism: A multicomponential analysis

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Abstract

Even though early treatment of congenital hypothyroidism (CH) with newborn screening prevents the mental retardation previously seen in cretinism, affected children still exhibit subtle persisting neurocognitive deficits. One of their commonest problems is poor attention, which reflects both early disease severity and later (high) circulating thyroid hormone levels. While attention is currently regarded as multicomponential in nature, with different processing components supported by different brain regions, the specific components of attention affected by CH have not been identified. In light of animal evidence showing that neonatal thyroid hormone deficiencies impede the neurodevelopment of structures important for selective aspects of attention, we proposed a multicomponential approach to study attention in children with CH. This was accomplished via retrospective analysis of existing data on adolescents with CH whose attention was previously evaluated using multiple tests. Results showed significantly poorer overall attention in CH than controls with differences occurring mainly on *focus* and *inhibit* indices. However, performance on various indices was associated with different disease parameters. Poor *encode* and *focus* were correlated with more severe hypothyroidism and a longer period of thyroid hormone insufficiency and poor *select* and *shift* with higher thyroid hormone levels at testing. These results signify that thyroid hormone is important for the development and later regulation of brain structures supporting distinct aspects of attention. (*JINS*, 2001, *7*, 734–744.)

Keywords: Attention, Congenital hypothyroidism, Thyroid hormone, Focus, Concentrate

INTRODUCTION

Congenital hypothyroidism (CH) is a disorder that affects about 1 in 3,500 children and occurs from insufficient thyroid hormone in infancy due to a missing or defective thyroid gland (La Franchi, 1999). Because thyroid hormone is extremely important for early brain development, extensive brain damage and mental retardation arise if CH is not promptly treated, a condition known as cretinism. Previously, early treatment of CH was not possible due to the late presentation of CH symptoms. Now, with the advent of newborn thyroid screening, these children are diagnosed and treated much earlier in life (Rovet, 1990). While this is sufficient to prevent mental retardation, affected children still attain IQs below expectation (Derksen-Lubsen & Verkerk, 1996) and are at risk for neuropsychological impairment (Rovet, 1999a). Specific deficits include problems in language (Gottschalk et al., 1994; Rovet et al., 1992), visuospatial abilities (Leneman et al., 2000; Rovet, 1999b; Salerno et al., 1999), neuromotor skills (Fuggle et al., 1991; Kooistra et al., 1994), memory (Rovet & Ehrlich, 1995), and attention (Kooistra et al., 1996; Rovet & Alvarez, 1996a). Their attention problems reflect etiology and severity of disease (Kooistra et al., 1996) as well as abnormal thyroid hormone levels at time of testing (Rovet et al., 1995).

Studies based mainly on rodents have shown that thyroid hormone is essential for early brain development and subsequent brain function (Bernal & Nunez, 1995; Porterfield & Hendrich, 1993). Thyroid hormone plays a role in several major neurobiological events including neurogenesis, neuronal migration, axon and dendrite formation, synaptogenesis, and myelination (Porterfield & Stein, 1994). Because the requirements for thyroid hormone are localized in selective structures (Bradley et al., 1989), which also differ

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as to when they need thyroid hormone (Bradley et al., 1992), the effects of a lack of thyroid hormone vary depending on timing. Structures that are highly thyroid hormone dependent include the parietal cortex, hippocampus, and caudate, which are important for different aspects of attention (Mirsky et al., 1991).

In addition to its role in structural brain development, thyroid hormone is also important for neurotransmitter regulation (Claustre et al., 1996; Gould & Butcher, 1989; Virgili et al., 1991) and, in fact, thyroid hormone purportedly acts as a co-transmitter (Rozanov & Dratman, 1996). Findings indicate that low levels of thyroid hormone are associated with elevations of dopamine and norepeinephrine while high levels suppress catecholamine activity (Mano et al., 1998). Because catecholamines are important for attention (Tucker & Williamson, 1984), especially reactivity to novelty (i.e., focused attention; Posner & Petersen, 1990) and inhibitory control (Pliszka, et al., 1996), and because they are dysregulated in individuals with attention disorders (Ernst et al., 1994; Malone et al., 1994; Mefford & Potter, 1989), it is not surprising that attention is compromised when thyroid hormone levels are abnormal. For example, Hauser et al. (1993) reported that up to 80% of children with resistance to thyroid hormone, a genetic disorder caused by a mutation in a thyroid receptor gene, had attention deficit hyperactivity disorder (ADHD). Individuals with hyperthyroidism also demonstrate poor attention that improves to normal when euthyroidism is achieved (Alvarez et al., 1983; Bhatara & McMillan, 1998; Whybrow et al., 1969). In pediatric hyperthyroid patients, attention problems are selective for disengaging and shifting attention, whereas the ability to sustain attention is unaffected. Among children with acquired hypothyroidism, attention is problematic only after initiation of therapy (Rovet et al., 1993a) and is thought to represent a hypercatecholaminergic reaction from introduction of exogenous hormone (Rovet & Daneman, 1998).

Likewise, children with ADHD can also have abnormal thyroid hormone levels (Spencer et al., 1995; Valentine et al., 1997; Weiss et al., 1993), which vary in relation to medication status. Findings from our lab showed that thyroid hormone levels were consistently in the low end of the normal range in children with ADHD being treated with methylphenidate but tested off medication (Bass et al., 1996) and that their thyroid hormone levels normalized on medication (Diamond et al., 1998). Moreover, selective aspects of attention appeared to be compromised by low thyroid hormone levels in these children (Rovet & Cole, 1999).

In children with CH, perturbations in levels of circulating thyroid hormones are seen during childhood (Germak & Foley, 1990; Hanukoglu et al., 2001; Heyerdahl & Kase, 1995) and attributed to infrequent monitoring (especially during periods of increased growth) and over- or undertreatment (New England Congenital Hypothyroidism Collaborative, 1994; Van Vliet, 1999). These perturbations have been associated with poorer cognitive abilities (Heyerdahl et al., 1991; Rovet & Ehrlich, 1995), including poorer attention (Rovet & Alvarez, 1996a, 1996b). Rovet and Alvarez showed that even among closely monitored cases with CH, only one-third of the children actually had thyroid hormone levels in the normal range at time of testing, with the majority demonstrating compensated hypothyroidism (i.e., elevated thyrotropin or TSH levels with normal thyroxine levels) or thyroid hormone resistance (elevated thyroxine with normal or elevated TSH). Children with the resistant pattern scored lowest on attention tests, particularly tests requiring them to encode information.

In neuropsychology, attention is typically seen as cognitive processes that serve to enhance or facilitate mental processing. Different processes appear to involve distinctly different brain regions (Mirsky et al., 1991; Stuss et al., 1995). Several models that specify the neuroanatomic correlates of different attention processes have been proposed. According to Mirsky et al. (1991), attention is represented by *focus/execute*, *encode*, *sustain*, and *shift* processes, which are supported by superior temporal and inferior parietal cortices, hippocampus, subcortical structures, and prefrontal cortex respectively. The model of Stuss et al. (1995) distinguishes mainly among anteriorly represented attention processes (e.g., *shift, inhibit)*. Because animal studies indicate that some of the structures described by these models are also impaired by neonatal hypothyroidism (e.g., parietal cortex, hippocampus, caudate; Bernal & Nunez, 1995; Porterfield & Hendrich, 1993), this has implications for the types of deficits that children with CH will encounter.

While children with CH are found to demonstrate selective attention problems, particularly in focused and sustained attention (Kooistra et al., 1996), their full range of their attention deficits has not been examined. Recent studies in the pediatric literature have used a multicomponential approach to investigate attention in children with disorders such as diabetes, head injury, Tourette's syndrome, and hyperthyroidism (Alvarez et al., 1996; Anderson et al., 1998; Ewing-Cobbs et al., 1998; Loss et al., 1998; Rovet & Alvarez, 1997; Yeates & Bornstein, 1994). For example, the study on children with hyperthyroidism by Alvarez et al. (1996) demonstrated difficulties in *shifting and disengaging* but not *sustaining* attention during thyrotoxicosis (i.e., elevated thyroid hormone levels) and adequate performance in all aspects when thyroid hormone levels normalized. Of clinical relevance, Loss et al. (1998) also showed that different aspects of achievement were predicted by selective components of attention.

The present paper uses a multicomponential approach to study attention in children with CH who, as part of their neuropsychological evaluation at adolescence (Rovet, 1999a), received multiple tests of attention. Because these adolescents were also assessed for academic achievement, a supplementary goal is to study the impact of selectively poorer attention in different aspects of school achievement. The following questions will be addressed: (1) Is early-treated CH associated with selectively poorer attention at adolescence? (2) What factors relating to early hypothyroid-

ism and current thyroid hormone levels affect specific aspects of attention? (3) What are the clinical implications (in terms of school achievement) of selectively poorer attention?

Based on animal studies showing that neuroanatomic structures underlying *focus* and *encode* aspects of attention were impaired by insufficient thyroid hormone during the neonatal period, we hypothesized that these aspects of attention would be most compromised by severe hypothyroidism at birth. Also, given thyroid hormone's putative role in catecholamine production and the role of catecholamines in reactivity to novel stimuli (i.e., focused attention) and inhibitory control, we secondly hypothesized that the *focus* and *inhibit* facets of attention would be affected by low levels of thyroid hormone at testing (seen in ADHD) and *shift* by high levels (seen in hyperthyroidism). Since children with CH who showed the resistant hormonal profile did more poorly on *encode*, this aspect of attention would also be affected by elevated thyroid hormone levels. Given Loss et al.'s findings that different components of attention predicted aspects of achievement (Loss et al., 1998), we thirdly hypothesized that variations in attention subcomponents in children with CH would be associated with poorer ability in selective academic areas.

METHODS

Research Participants

The sample consisted of 49 adolescents (13 male) who were seen at a mean age of 13.9 ± 1.3 years and included 13 children with a missing gland (athyrosis), 23 with a dysgenetic gland that was ectopic or hypoplastic, and 13 with dyshormonogenesis. All children were diagnosed with CH at birth through the Ontario newborn-screening program. They belonged to a larger cohort of 106 cases that we followed over the course of childhood, most since birth. The present group represented those from the original cohort who had reached the age of 13 years between 1993 and 1996, could be located, and were willing to participate. While details of their early development and hypothyroidism are provided in Rovet (1999b), it should be noted that all were identified and treated early in life (M = 16.25 days) with an adequate dosage of replacement hormone (mean starting dose = 9.3 + 5 mg/kg). At time of testing, their mean level (±*SD*) of triiodothyronine (T3) was 2.1 ± 5.0 nmol/l (normal range = 2.5–4.8), thyroxine (T4) was 113.8 ± 31 μmol/l (normal range = 65–156) and TSH was 6.7 ± 9.11 mU/l (normal range = 0.5–5.0 mU/l) with 33% of study participants having elevated TSH levels.

Controls were drawn from a large control pool that was similarly tested. This pool also included 18 adolescent siblings of children with CH, whom themselves were too young to take part presently. Controls were selected to match each participant with CH for gender and age at time of testing. They had a mean age of 14.0 ± 1.4 years and included 13 boys and 36 girls.

Approval for this component of the research was obtained from the Research Ethics Board of The Hospital for Sick Children.

Tests and Measures

The tasks were provided as part of a comprehensive neuropsychological test battery given at adolescence and are described elsewhere (Rovet, 1999b). Intelligence was tested with the Wechsler Intelligence Scale for Children–Revised (WISC–R, Wechsler, 1974) and achievement with the Wide Range Achievement Test–Revised (WRAT–R, Jastak & Wilkinson, 1984), with the older test versions being used since the current versions were not available when this component of the research began. Table 1 describes the specific attention tests and relevant parameters for this study. Information about attentional functioning was additionally obtained from the Child Behavior Checklist completed by parents (Achenbach, 1991a) and the Youth Self Report Inventory completed by the adolescents (Achenbach, 1991b).

In the current CPT version (Garfinkel & Klee, 1983), the computer monitor showed 700 colored alphabetic characters one at a time at a fast rate (100 ms) with a brief interstimulus interval between them set according to the participant's age. The task was to press the space bar whenever a white 'S'–blue 'T' combination appeared. Stimuli were presented in seven blocks each containing 10 target pairs (20% trials), 20 other 'S–T' color combinations (40% trials), and 40 other letter–color combinations. This CPT version provided a detailed analysis of specific commission errors according to timing of response and whether the error was to the first or second stimulus and to the color or the letter feature.

From each child's medical chart, information was obtained regarding etiology of hypothyroidism, bone age at diagnosis, hormone levels at diagnosis, age at treatment onset and starting dose level, and hormone levels (T3, total T4, and TSH) on day of testing. In addition, parent IQ and socioeconomic status (SES) were determined during an earlier phase of the research (see Rovet et al., 1992).

Data Management and Analyses

Composite variables for nine unique aspects of attention processing were determined using averaged *z* scores of relevant attention indices as listed in Table 2. The particular combinations were based on task analysis and the distinctions described by Mirsky et al. (1991), Stuss et al. (1995), and Posner and Gilbert (1999). A principal components factor analysis with a varimax rotation was used to confirm these distinctions.

Groups were compared using MANCOVA and *t* tests with the Bonferroni *p*-correction applied. The relations between thyroid hormone levels and specific attention subcomponents and between attention and achievement were examined via Pearson product-moment correlations and multiple regression analyses.

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Table 1. Attention battery

Name of instrument	Task requirements	Variables, measures
CPT (Garfinkel & Klee, 1983)	Colored letters are successively shown on computer monitor; participant responds to white 'S'–blue 'T' combinations only (see text for more details).	Omission & commission errors, change over blocks.
MMFFT (Rovet, 1980)	Participants are shown a line drawing of a target picture and 2 to 8 highly similar response variants; their task is to locate as fast as possible the variant matching the target.	Mean errors/item, mean RT for first response, error & RT slopes.
Stroop (Stroop, 1935)	Provided via three sheets of paper each containing 100 stimuli: color names printed in black ink, 'X's shown in different ink colors, and color names printed in an incongruent color. Participants are given 45 s to read as many color names and state the colors of the 'X's and colors of inks as possible.	Color rate & T-value for colors, words, and word colors, interference.
Trails A and B (Reitan, 1958)	Provided via two sheets of paper, participants first connect randomly arrayed numbers (Trails A) and then alternating numbers and letters (Trails B).	Time to completion
Object Identification Task (Kimura et al., 1981)	Participant is shown a large wooden board containing 84 line drawings of common objects. Cards are placed in the center of board depicting one of the objects and task is to find it on the board.	Mean RT/item.
WCST (Heaton, 1981)	Participants sort stimulus cards of varying color, shape, and number. Feedback is provided for the correct sorting principle and after a specified number of sorts, principle is changed and subject must learn new rule.	Errors, categories, perseverative errors.
WISC–R Arithmetic, Digit Span, Coding subtests (Wechsler, 1974)	Arithmetic requires computation of mental arithmetic word problems; Digit Span, the repetition of increasingly larger digit lists in first forward and then reverse orders; Coding, the learning of number-symbol combinations and copying the symbols in a page of provided numbers.	Scaled score.

CPT = Continuous Performance Test; MMFFT = Modified Matching Familiar Figures Test; WCST = Wisconsin Card Sorting Test.

RESULTS

Demographics

A comparison of study participants and children from the original cohort who were not participating presently indicated the groups were comparable in terms of disease etiology and severity, treatment, parent IQ, and SES (see Table 3).

Intelligence, Achievement, and Behavior

Intelligence and achievement test results of CH and control groups are shown in Table 4. The results indicated that the CH group scored significantly below controls on Verbal IQ ($p < .05$), Performance IQ ($p < .0001$), and Full Scale IQ ($p < .001$) and Vocabulary, Picture Completion, and Block Design subtests of the WISC–R ($p < .01$). Groups did not differ in terms of achievement. On the CBCL (data not shown), parents rated children with CH significantly higher in Total Behavior Problems ($p < .05$), with 10% of children with CH *versus* zero percent of controls obtaining scores in the significantly elevated range. CH children also differed from controls on the Anxiety Depression ($p < .01$), Attention Problems ($p < .001$), Delinquent Behaviors ($p < .01$), Thought Problems ($p < .01$), and Withdrawal ($p < .01$) scales. Examination of individual items from the Attention scale revealed that "problems concentrating" was the most common complaint. Groups did not differ in achievement or on the Youth Self Report.

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Table 2. Specification of attention components and their putative neuroanatomic substrates

Attention component	Definitions of attention components	Task variables	Representative factor[a]	Putative neuroanatomic substrates
Detect	Respond to an intermittent stimulus	CPT omission errors	F1	Cingulate[b]
Encode	Register and recall sequential information	WISC–R Digit Span & Arithmetic scaled scores	F1	Hippocampus[c]
Focus	Select target information for enhanced processing	WISC–R Coding scaled score & Trails A RT	F2	Inferior parietal & superior temporal cortex, striatum[c]
Inhibit	Withhold a prepotent response	CPT commission errors	F1	Dorsolateral prefrontal cortex[c]
Search	Find target in complex or busy array	Object Identification RT	F4	Extrastriate cortex[d]
Select	Choose a specified object from several alternatives	MMFFT mean errors	F2	Orbitofrontal prefrontal cortex[b]
Shift	Change attentional focus between stimuli	Trails B RT & WCST perseverative errors	F2	Medial frontal cortex[a,b]
Suppress	Withhold interference from distracting stimuli	Stroop interference score	F1	Dorsolateral prefrontal cortex[b]
Sustain	Maintain focus and alertness over time, be vigilant	CPT change score	F3	Reticular formation[c]

[a]Based on findings from factor analysis. Shown here are the factors on which each of the attention variables loaded most highly; [b]Based on Stuss et al., 1995; [c]Based on Mirsky et al., 1991; [d]Based on Posner & Gilbert, 1997.

Attention

Table 5 presents the results from the attention tests. CH and control groups differed on the CPT, Trail Making, and WCST but not MMFFT, Object Identification, or Stroop (see Table 5). On the CPT, CH adolescents made significantly more commission errors ($p < .01$) and, on Trail Making responded significantly more slowly than controls on Trails A ($p < .01$) but at the same rate on Trails B. On the WCST, the CH group was less accurate than controls ($p < .01$) but made fewer perseverative errors ($p < .01$) while using the same number of categories. On the WISC–R Freedom From Distractibility subtests, CH showed a trend for lower scores than controls on Coding ($p = .058$, see Table 4) but not Arithmetic or Digit Span.

A supplementary analysis of individual CPT errors showed that the CH group made a specific type of commission error. Rather than responding impulsively to the appearance of either target stimuli, they erred mainly on a feature of the first stimulus, especially its color, as shown in Table 6.

Analysis across the nine attention components using MANCOVA (age as a covariate) revealed a highly significant omnibus group difference [$F(9,86) = 4.22$, $p < .001$]. Univariate analyses indicated significant differences on *focus* ($p < .001$), *inhibit* ($p < .01$), and *shift* ($p < .05$) components. As shown in Figure 1, the CH group was less able than controls to *focus* and *inhibit* but tended to *shift* more easily.

Factor analysis for the nine attention variables for the control participants identified four unique factors (see Table 2). Factor 1, accounting for 55% of the variance (Eigenvalue = 8.31), included *inhibit*, *suppress*, *detect* abilities, and to a lesser degree, *encode*; Factor 2, accounting for 25.5% of the variance (Eigenvalue = 3.83), included *select* and *shift* and to a lesser degree *focus*; Factor 3 accounting for 10.6% of the variance (Eigenvalue = 1.59) included *sustain*; and Factor 4 accounting for 8% (Eigenvalue = 1.27) included only *search*. A MANCOVA on factor composite scores showed a significant omnibus group effect ($p < .05$), which reflected the marginally lower scores on the first factor by the CH group [$F(1,92) = 3.00$, $p < .09$].

Biomedical Correlates of Attention in CH

Using MANCOVA, we also compared children with CH on the nine attention variables according to their etiology of hypothyroidism. Although these CH subgroups did not differ overall, significant univariate effects were found for *encode* [$F(2,44) = 3.89$, $p < .05$] and *shift* [$F(2,44) = 3.81$, $p < .05$]. Children with athyreosis or ectopic glands performed more poorly than those with dyshormonogenesis on *encode* while children with athyreosis performed more poorly than both of the other etiologies on *shift* (see Table 7).

For the CH group only, correlations were computed between demographic and biomedical parameters and the nine attention variables. Different attention variables were predicted by background factors *versus* biomedical indices.

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Table 3. Comparison between participants and nonparticipants with CH

	Participants		Nonparticipants	
Variable	*M*	*SD*	*M*	*SD*
Etiology (% athyrosis)	33.3		28.6	
Bone age (weeks)	37.2	2.4	36.0	3.9
T4 at diagnosis (μmol/L)	75.5	57.6	70.5	199
TSH at diagnosis (mM/U)	138.3	103.4	131.2	119.7
Severity score	.077	.60	.080	.51
Treatment age (days)	17.3	20.4	16.3	20.4
Dose (μg/kg)	7.44	1.24	7.06	2.0
Parent IQ	103.0	13.0	97.7	17.9
SES	41.6	12.0	42.1	15.3

Parent IQ correlated ($p < .01$) significantly with *detect* and *search* [$r(37) = .40$ and 38], and marginally with *select* [$r(37) = .32$, $p = .06$], while SES was correlated with *sustain* [$r(45) = -.36$, $p < .05$]. As a rule, the higher the parental IQ, the better the child did on *detect*, *search*, and *select* components while the higher the SES, the less able they were to sustain attention. Regarding biomedical indices, better *encode*, *focus*, and *shift* abilities were associated with more advanced bone ages at diagnosis (signifying later onset of hypothyroidism) [$r(37) = .37, .35,$ *and* $.38$, $p < .05$]; better *shift* with an earlier age at starting treatment [$r(47) = -.27$, $p < .05$]; and better *suppress*, with a lower starting dosage [$r(37) = -.32$, $p < .05$]. Duration of hypothyroidism was negatively correlated with *focus* and *shift* [$r(37) = -.49$ *and* $-.47$, $p < .01$], with adolescents who took longer to achieve normal thyroid hormone levels in infancy scoring lower on both parameters. Higher T4 levels at time of testing were associated with significantly poorer *search* [$r(47) = -.28$, $p < .05$], and a trend for poorer *select* ($p < .10$). T3 and TSH levels at time of testing were unrelated to attention. For each of the nine attention variables, multiple regression analyses were computed with age at testing, parent IQ, disease severity, treatment age, duration of hypothyroidism and T4 level at testing as predictors. Results revealed a significant omnibus effect only for *shift* [$F(6,29) = 2.64$, $R^2 = .338$], reflecting (1) the negative effect of delay in treatment onset and (2) the positive effect of higher T4 levels at testing. A near significant trend for *focus* ($p < .10$, $R^2 = .275$) reflected the worse outcome the longer the delay in normalization thyroid hormone levels.

Table 4. Intelligence and achievement test results

	CH		Control		
Measure	*M*	*SD*	*M*	*SD*	*p*
Intelligence					
Verbal IQ	99.4	10.5	104.1	12.4	.05
Performance IQ	104.0	15.8	115.0	11.8	.001
Full Scale IQ	101.6	12.8	110.0	11.2	.001
Vocabulary	8.8	1.9	10.1	2.6	.01
Similarities	10.4	2.1	11.1	2.0	.09
Arithmetic	10.7	2.8	11.2	3.3	n.s.
Digit Span	10.0	2.6	10.8	3.1	n.s.
Picture Completion	9.7	2.7	11.6	2.9	.001
Block Design	10.7	2.8	12.7	2.3	.01
Coding	10.9	3.5	12.1	2.8	.058
Achievement					
Reading	70.6	29.3	63.4	29.4	n.s.
Spelling	58.4	25.9	53.6	27.4	n.s.
Arithmetic	41.6	24.9	42.6	27.4	n.s.

[a]Percentile scores.

Effects of Attention on Achievement

To examine how variations in specific components of attention affected achievement, separate multiple regression analyses were computed for the three achievement subtests using the nine attention variables (listed in Table 2) as well as age at testing and group status (CH or control) as predictors. Reading was predicted by *encode* ($p < .001$), Spelling by *encode* ($p < .001$) and *select* ($p < .05$), and Arithmetic by *shift* ($p < .05$), *select* ($p < .05$), and *suppress* ($p < .01$). There were no effects of age or group status in the regressions.

DISCUSSION

This research was prompted by studies involving both experimental animals and patients with various forms of thyroid disease. The animal studies showed that neuroanatomic structures critical for certain aspects of attention (e.g., the ability to respond to oncoming visual stimuli and to register events as they happen) are disturbed if thyroid hormone levels are inadequate in early life (Porterfield & Stein, 1994) and that catecholamines, which are important in regulating attention, are sensitive to ambient levels of thyroid hormone (Mano et al., 1998; Savard et al., 1983; Virgili et al., 1991). Findings on various patient groups also showed that

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Table 5. Attention test results

	CH		Control		
Test result	*M*	*SD*	*M*	*SD*	*p*
CPT					
Omission errors	17.6	12.2	17.0	10.3	n.s.
Commission errors	19.1	18.2	11.4	10.6	.01
Change	.067	.21	.090	.20	n.s.
MMFFT					
Errors	0.43	.31	.41	.32	n.s.
RT (s)	26.3	10.7	25.1	11.9	n.s.
Error slope	0.13	.17	.09	.16	n.s.
RT slope	2.43	2.0	3.07	3.0	n.s.
Object Identification Task	4.7	2.8	4.6	1.9	n.s.
Stroop					
Color Rate	1.59	.31	1.48	.20	n.s.
Word Rate	2.23	.35	2.17	.37	n.s.
Color of Word Rate	0.89	.20	0.92	.17	n.s.
Color T	43.5	9.2	43.3	6.0	n.s.
Word T	45.1	7.7	45.3	6.3	n.s.
Color of Word T	45.0	9.3	47.8	8.4	n.s.
Interference	−0.82	6.7	−0.10	15.0	n.s.
Trail Making Test					
Trails A	21.4	13.4	15.1	7.3	.005
Trails B	39.8	25.4	33.7	17.2	n.s.
WCST					
Accuracy	62.7	6.3	66.9	9.5	.01
Errors	11.4	15.6	19.5	13.9	.01
Categories	5.7	1.0	5.4	1.0	n.s.
Perseverative Errors	4.3	5.8	10.1	6.7	.001

insufficient thyroid hormone levels early in life (as in CH) contributed to poorer focused and sustained attention while variations in thyroid hormone levels later affected several other attentional functions.

The present study used a multicomponential approach to identify attentional subcomponents sensitive to early thyroid hormone insufficiencies and later variations in thyroid hormone levels. We first hypothesized that insufficient thyroid hormone levels early in life would affect attention selectively. Because the brain structures compromised by a lack of thyroid hormone are important for *focus* and *encode* aspects of attention, we predicted that these processes would be especially weaker in children with CH. Present results provide partial support for this hypothesis: children with CH did perform more poorly than controls on *focus*, but not *encode* attention indices, and also on *inhibit* (supported by dorsolateral prefrontal cortex), contrary to prediction. While the lack of finding for *encode* was based on digit span tasks, supplementary analyses of their CPT error profiles, which ostensibly reflected problems of inhibitory control actually suggested that a short-term memory problem was underlying this poor performance because they were more likely to

Table 6. Analysis of commission errors on the CPT

	CH		Control		
Error type	*M*	*SD*	*M*	*SD*	*p*
Error to letter of 1st item	1.20	2.18	0.37	.78	<.01
Error to color of 1st item	2.49	2.84	1.00	1.10	<.001
Error to 1st item	3.78	4.8	1.37	1.64	<.001
Error to letter of 2nd item	4.08	3.9	3.25	4.0	n.s.
Error to color of 2nd item	4.69	4.7	3.12	3.1	n.s.
Error to 2nd item	8.29	8.0	5.71	7.1	n.s.
Random errors	3.14	5.18	3.33	3.09	n.s.

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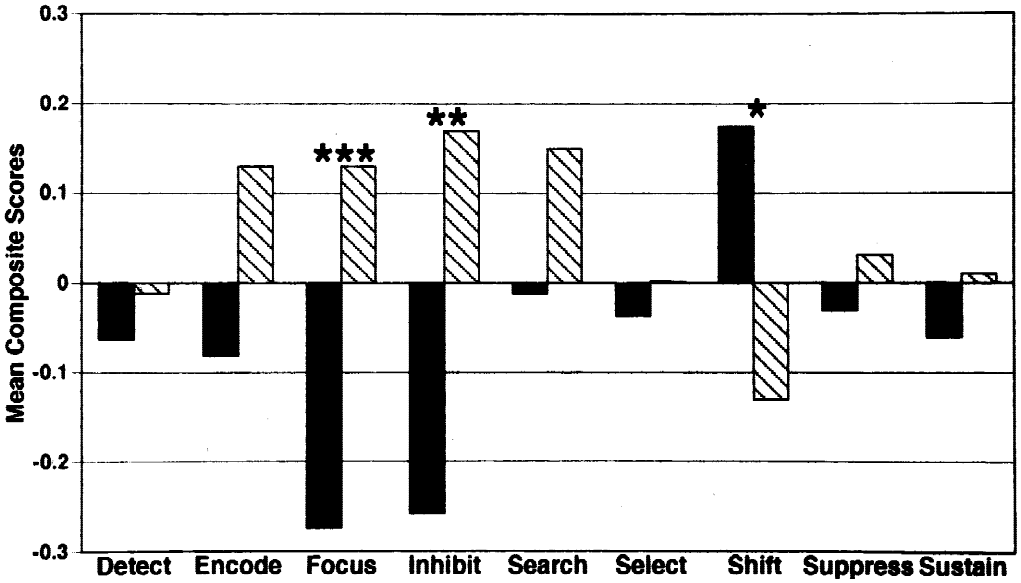

Fig. 1. Mean standardized scores for attention components in adolescents with congenital hypothyroidism (black bars) and normal controls (striped bars). Differences were significant at the $p < .001$ level for *focus*, at the $p < .01$ level for *inhibit*, and at the $p < .05$ level for *shift*.

respond incorrectly to a feature of the first than the second stimulus. This signifies greater difficulty registering incoming information than controlling impulsivity. Also given that the results indicated correlations between indices of early disease severity and duration and *encode*, this suggests that thyroid hormone appears to play a role in the development of substrates such as hippocampus and caudate, which supports this ability.

The second hypothesis concerned whether higher thyroid hormone levels at time of testing adversely affects frontally mediated aspects of attention (i.e., *shift*, *suppress*, *inhibit*). Again, results provide only partial support for this hypothesis with high concurrent T4 levels correlating with poorer performance on *shift* and *select* but not *inhibit* attention processes.

The third hypothesis, which concerned the clinical relevance of variations in different aspects of attention on achievement, was tested by regressing the attention variables on indices of achievement. Results revealed that *encode* was important for Reading and Spelling, *select* for Spelling and Arithmetic, and *shift* and *suppress* for Arithmetic. Children who did better on *encode*, *select*, and *suppress* had higher achievement scores, whereas children who did better on *shift* scored lower in arithmetic. As these attention variables also correlated with different aspects of the disease and its treatment, this suggests the need for prudent detection and management of CH. The finding that time to normalization was the strongest predictor of *focus* and *shift* suggests that early and optimal therapy is essential for good outcome.

An intriguing finding from the error analysis of the CPT concerns the increased number of commission errors by children with CH. These do not reflect an inability to *inhibit* attention but rather a greater likelihood of missing a

Table 7. CH subgroups by etiology of hypothyroidism on variables of attention

	Athyrotic		Ectopic		Dyshormonogenesis		
Attention variable	*M*	*SD*	*M*	*SD*	*M*	*SD*	*p*
Detect	−.123	.35	−.295	.23	.434	.18	n.s.
Encode	−.154	.12	−.385	.19	.541	.30	.01
Focus	−.610	.23	−.243	.21	.090	.16	.10
Inhibit	−.223	.29	−.476	.31	.133	.18	n.s.
Search	−.042	.26	−.067	.23	.135	.20	n.s.
Select	.028	.13	−.082	.15	−.034	.22	n.s.
Shift	−.236	.19	.286	.12	.417	.18	.01
Suppress	.103	.14	−.025	.14	.043	.15	n.s.
Sustain	−.10	.21	.08	.19	−.27	.40	n.s.

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critical feature of the first stimulus in the pair, suggestive of a memory problem. While memory problems have been reported previously in this population (Rovet & Ehrlich, 1995), analyses of their specific memory problems have not been described. Current work in our lab using both new clinical memory instruments for children and computer-based memory tasks may serve to unravel their specific memory deficits. A *post-hoc* analysis of their performance on a variety of memory tests conducted as part of the current assessment suggested these children had greater difficulty with episodic than semantic components of memory (Rovet & Cole, 1999). Following the assumption that episodic memory involves the hippocampus (Vargha-Khadem et al., 1997), this suggests that thyroid hormone is probably essential (during gestation and early life) for optimal hippocampal formation and subsequent episodic memory.

Another interesting result reflects the findings of the factor analysis (Table 2), which combined seemingly disparate attention variables believed to be supported by distinct and often distant brain regions. Abilities comprising the first factor involved the hippocampus, cingulate, and dorsolateral prefrontal cortex as a unit, while those comprising the second factor involved striatum, posterior cortices, orbitofrontal and medial lateral prefrontal cortex. These findings suggest the possibility of discrete neural networks in attention functioning that may be selectively disrupted by insufficient thyroid hormone at critical stages of neurodevelopment. Comparison of CH with controls revealed they differed mainly on Factor 1 and so possibly the hippocampus, cingulate, dorsolateral prefrontal cortex network.

The present study is limited by using clinical instruments to assess specific attention components and drawing inferences from them about the development of specific brain regions. Although the instruments used presently were valid and reliable measures of attention, most were not developed as measures of specific attentional subcomponents. In addition, assignment of selective test variables as specific attention processes was *post hoc*, even though this method was based on prior studies that used comparable tests and a similar approach (e.g., Mirsky et al., 1991) and was substantiated using factor analysis. Furthermore, the assumption of regional specialization does not account for the complex neural circuits that are involved in attention, as represented by the common factor in Table 2. Ultimately, neuroimaging studies will be useful in identifying abnormalities in development and differences in regional activation. Differences from normal children in coactivated regions may be suggestive of weakness in specific circuits.

Further studies to examine distinct components of attention directly are therefore required. In our lab, a recent study used computer-generated attention tasks designed to tap specific aspects of attention directly showed that children with CH have a deficit in their ability to *focus* attention and are lagging in their development of *select* and *search* processes (Rovet & Cole, 1999). In contrast, children with ADHD who were given the same tasks did more poorly than controls on *focus*, *search*, *inhibit*, and *suppress* components of attention. In the CH group, high thyroid hormone levels at time of testing were correlated with poorer attention, whereas in ADHD (whose TH levels were also determined on day of testing), lower TH levels were associated with poorer *sustain* and *focus* attention but not *inhibit* or *suppress*.

A final concern is why the *shift* function is better in children with CH than controls, even though *shift* was negatively correlated with indices of hypothyroidism severity. Although its significance is not readily clear, this effect may be an artifact of the WCST paradigm. Even though our children with CH made fewer perseverative errors, they were in fact less accurate overall on this task than controls. Unfortunately, as we did not record other types of errors, we have no way of accounting for their poorer performance on this task. A positive association was observed between *shift* and arithmetic achievement suggesting that children who shifted more readily did do better in this domain. These findings signify that frontal functions are not adversely affected by early hypothyroidism, consistent with the animal literature reporting that abnormalities occur in this region only if thyroid hormone insufficiencies took place relatively late in infancy (Gould & Butcher, 1989).

In summary, the present study showed that adolescents with CH perform below controls in selective aspects of attention and this reflects early disease severity, duration of hypothyroidism, and thyroid hormone levels on day of testing. Primarily affected by CH were the abilities to *focus* and *encode* oncoming information. Because more severely affected attention processes (i.e., *focus* and *encode*) were those subserved by brain structures known to develop abnormally in hypothyroid animals, this suggests potentially similar involvement of thyroid hormone in human brain development. In addition, we found that high thyroid hormone levels at time of testing contributed to poorer attention searching large arrays and, to a lesser extent, identifying a target from among highly similar alternatives. As these are thought to involve more frontally mediated attention processes (Stuss et al., 1994), elevated levels of thyroid hormone at time of testing may interfere with neurotransmission, reflecting both production and regulation of catecholamines.

In conclusion, this study has shown that thyroid hormone appears to be essential for the development and subsequent regulation of selective aspects of attentional processing and presumably the underlying brain structures and systems. Furthermore, congenital hypothyroidism appears to be a good model to study attention from a multicomponential perspective.

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