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# Visuospatial, Visuoperceptual, and Visuoconstructive Abilities in Congenital Hypothyroidism

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**Abstract**

Individuals with congenital hypothyroidism (CH), even those diagnosed and treated early, experience selective cognitive deficits, the most striking of which involves the visuocognitive domain. However, the range and nature of their visuocognitive disturbances is not fully understood. We assessed a range of higher-order visuocognitive abilities in 19 children and adolescents with CH and 19 age- and sex-matched typically developing peers (TD) using a battery of neuropsychological tests and a novel self-report measure of sense of direction. CH scored lower than TD on direct tests of visuocognitive function (judging line orientation, parts-to-whole localization, copying three-dimensional block towers, discriminating designs, and matching unfamiliar faces in $\frac{3}{4}$ profile-view) as well as on self-reported problems in spatial ability. Visuocognitive problems were not global as CH and TD did not differ at copying two-dimensional block designs, mentally rotating and matching abstract shapes, or at matching unfamiliar front-view faces, design features, or designs that engaged either figure-ground segregation, visual constancy, or closure. Early and concurrent thyroid stimulating hormone (TSH) levels were associated with visuocognitive ability, although attention and working memory were not. Individuals with CH exhibit selective visuocognitive weaknesses, some of which are related to early and concurrent TSH levels. (*JINS*, 2013, *19*, 1119–1127)

**Keywords:** Visuospatial, Sense of direction, Congenital hypothyroidism, Thyroid hormone, Attention, Working memory

## INTRODUCTION

Congenital hypothyroidism (CH) is a pediatric endocrine disorder affecting 1 in 2500 newborns (Harris & Pass, 2007) that arises from insufficient thyroid hormone (TH) production. Despite early diagnosis via newborn screening and optimal care, affected children with CH still exhibit a variety of subtle motor and cognitive weaknesses that are directly linked to their early TH insufficiency, which begins as early as the third trimester and may last until the second month of life (Fuggle, Grant, Smith, & Murphy, 1991; Kempers et al., 2006; Rovet, 2002). These include problems in sensorimotor function (Rovet, 2002), hippocampally mediated memory (Willoughby, McAndrews, & Rovet, 2013), attention (Kooistra, van de Meere, Vulsma, & Kalverboer, 1996), and visuocognitive abilities (Rovet, 2002).

Of all the domains of function affected by CH, visuocognitive disturbances are the most striking, showing the greatest difference from typically developing peers (Rovet, 1999a). However, the precise nature of the specific visuocognitive impairments contributing to their poor performance on clinical tests is not well understood because most studies report composite scores derived from tests that assess a variety of visuocognitive processes (e.g., Rovet, 1999a). Given evidence from neuroanatomic and neuropsychological studies supporting segregation of higher-order visual function (Ungerleider & Haxby, 1994), neuropsychologists have classified higher-order visual tests according to the extent that they engage visuoperceptual, visuospatial, and visuoconstructive abilities (Lanca, Jerskey, & O'Connor, 2003). Visuoperceptual abilities refer to those processes involved in analysis and identification of visual stimuli for object recognition; visuospatial abilities refer to those processes involved in perceiving spatial location, orientation, direction, and distance; visuoconstructive abilities refer to the skills needed to put together parts to form a single whole (Stern, Rosenbaum, Fava, Biederman, & Rauch, 2008). Neuroanatomic studies support this tripartite division with distinct neural regions and connections between regions supporting distinct visuocognitive processes: Visuoperceptual

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processes have been localized to subregions within the temporal lobes including the fusiform face area (Kanwisher, McDermott, & Chun, 1997) and parahippocampal place area (Epstein & Kanwisher, 1998); Visuospatial abilities are supported by the caudal intraparietal sulcus (Sakata, Taira, Kusunoki, Murata, & Tanaka, 1997) and parts of the inferior parietal lobule, including the angular gyrus and posterior supramarginal gyrus (Tranel, Vianna, Manzel, Damasio, & Grabowski, 2009), as well as connections from the inferior parietal lobule to the medial temporal lobe (the so-called parieto-medial temporal pathway; see Kravitz, Saleem, Baker, & Mishkin, 2011); Visuocontructional abilities are mediated by parts of the superior parietal lobule, including areas V6A and the medial intraparietal area (Galletti, Gattori, Kutz, & Battaglini, 1997), and their connection to the premotor cortex (the parieto-premotor pathway; see Kravitz et al., 2011).

To date, no single study has comprehensively evaluated the full range of visuocognitive abilities in a single cohort of children and adolescents with CH, to clarify which abilities are affected by early TH insufficiency. Studies that looked at different visuocognitive measures in separate cohorts of children and adolescents with CH across varied age ranges have demonstrated that CH have difficulties with visuoperceptual abilities such as picture completion (Rovet, 1999b), visuospatial abilities such as judgment of line orientation (Leneman, Buchanan, & Rovet, 2001) and mental rotation (Blasi et al., 2009; Leneman et al., 2001), and visuoconstructive abilities such as block construction (Leneman et al., 2001; Rovet, 1999b) and object assembly (Blasi et al., 2009). However, studies demonstrate that some visuoperceptual abilities are intact in CH, such as matching figures (Blasi et al., 2009), memory for faces (Leneman et al., 2001), and object identification (Leneman et al., 2001). In particular, an important but understudied visuoperceptual process, face perception, has never been examined in children with CH.

Furthermore, no study has examined the "real-world" visuospatial functioning of children with CH (e.g., does the child report more difficulties navigating within a new environment or forget where he/she left things?). A novel self-report tool, the Santa Barbara Sense of Direction Scale (SBSDS; Hegarty, Richardson, Montello, Lovelace, & Subbiah, 2002), measures environmental spatial ability, which is involved in everyday tasks such as finding one's way around or learning the layout of a new environment. In adults, this scale was shown by Hegarty et al. (2002) to be related to the ability to update one's orientation and location in space with body movement in the environment. As such, the SBSDS provides a subjective measure of visuospatial ability outside of the laboratory. We adapted this questionnaire for use with children and adolescents to determine whether children with CH report more problems in spatial direction than their typically developing peers.

However the question remains as to why higher-order visual abilities would be vulnerable to TH deficiency. TH is essential for normal brain development (Farwell & Leonard, 2005) including development of the visual system. TH insufficiency affects development of structures from the retina (Kelley, Turner, & Reh, 1995), through the optic nerve (Baas, Legrand, Samarut, & Flamant, 2002), and into the primary visual cortex (Martinez-Galan, Escobar del Rey, Morreale de Escobar, Santacana, & Ruiz-Marcos, 2004). Berbel and colleagues (2010) have shown TH is also necessary for development of higher-order visual areas as evidenced by abnormal neuronal migration patterns within the parietal cortex, an area with a well-established role in spatial vision (Ungerleider & Mishkin, 1982) in TH-deficient rat pups. Although these structural abnormalities are likely linked to functional spatial deficits, this aspect of visual function has not been investigated in laboratory animals.

It is well established that performance on visuocognitive tasks may depend in part on abilities such as working memory and attention. While working memory is unimpaired, attention problems have often been reported in children with CH (Kooistra et al., 1996; Rovet, 1999a). The ability to focus and sustain attention is particularly affected in CH, whereas their abilities to inhibit, shift, and divide attention are unaffected (Rovet & Hepworth, 2001). Notably, performance on attention tests by children with CH is influenced more by their ambient TH levels (Rovet & Alvarez, 1996) than by early TH levels (Rovet, 2002). Importantly, abnormally low and abnormally high TH levels at time of testing are both associated with elevated scores on attention problem scales, suggesting that ambient TH levels, regardless of direction, contribute to suboptimal cognitive function (Rovet, 2002; Rovet, Daneman, & Bailey, 1993). The effect of ambient TH on higher-order visual abilities is not known despite the hallmark visuocognitive deficits exhibited by individuals with CH.

The primary aim of the present study was to describe the profile of visuocognitive abilities in a single cohort of children and adolescents with CH with documented early and concurrent TH levels. A supplementary aim was to determine whether attention and working memory were intact in CH and thus would not affect visuocognitive performance. Our second aim was to assess whether "real-world" visuospatial abilities are affected in CH and to assess the relation of ecological measures to direct tests of visuospatial processing. The final aim was to investigate the relation between TH levels (early and concurrent) and present visuocognitive function in CH, as well as between current TH levels and visuocognitive function in typically developing peers. Given the importance of visuospatial abilities for academic achievement, including both reading (Laycock & Crewther, 2008) and arithmetic (Delgado & Prieto, 1996), and for daily functioning, such as play and athletics, a better understanding of visuocognitive abilities in CH is timely.

## METHODS

### General Procedures

All testing took place in the Psychology Department at The Hospital for Sick Children (SickKids) over the course of one assessment. The human data included in this manuscript

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**Table 1.** Demographic characteristics of CH and TD participants

| | CH | TD | F ($\chi^2$) |
|---|---|---|---|
| Age (years) | 12.7 ± 2.5 | 13.3 ± 2.3 | .539 |
| Age range | 8.7 – 15.7 | 9.1 – 16.2 | |
| Sex | 10 male, 9 female | 10 male, 9 female | (.000) |
| SES | 2.0 ± 0.9 | 2.1 ± 1.1 | .118 |
| FSIQ | 107.7 ± 10.5 | 115.9 ± 9.3 | 6.667** |
| Vocabulary | 54.1 ± 8.1 | 61.0 ± 6.8 | 7.947** |
| Matrix reasoning | 55.2 ± 5.5 | 56.9 ± 6.3 | .821 |

*Note.* Age, SES, FSIQ, Vocabulary and Matrix Reasoning (T scores) are expressed as mean ± SD and were analyzed with ANOVA; sex was analyzed with chi-square. $^{**}p < .05$.

were obtained in compliance with the formal ethics review committee at the Hospital for Sick Children. Parents or guardians of participants provided signed informed consent while all children also gave assent before participating in the study. Total session time was 5 hours and included a battery of neuropsychological and experimental tests, and lunch and rest breaks. The tests were administered by two trained psychometrists (N.S., S.K.) and scored by three psychometrists (Rosie Bell, N.S., & S.K.). Following completion of the behavioral tests, each participant was invited to donate a small blood sample from which TH levels would later be assayed. Parents were reimbursed for travel and parking and participants received a movie gift certificate and a certificate of participation used for high school social credit hours.

## Participants

CH participants were all originally recruited from the Endocrine Division at SickKids. The majority were past participants in previous studies in the Rovet lab while a handful were newly recruited from the clinic. Of the 20 current participants, one who later received a secondary diagnosis of pseudoparahypothyroidism was excluded from subsequent analyses. The remaining 19 consisted of 9 females and 10 males with a mean age of 12.7 years and age range = 8.7–15.7 years. They were born between January 1994 and July 2001. Based on technetium scans at time of diagnosis, five CH had athyrosis, eight had ectopic glands, and three had dyshormonogenesis; three children had unknown etiologies because of parent refusal of the technetium scan ($n = 1$) or children were originally diagnosed in a hospital where scans were not routinely performed ($n = 2$). Across the entire group, the median newborn thyroid stimulating hormone (TSH) level was significantly elevated at 192.0 ± 98.0 mU/L (reference range = 0.5–5.0 mU/L; $n = 10$), their median TSH at diagnosis was also elevated at 433.1 ± 326.7 mU/L ($n = 15$), their mean thyroxine (T4) was 67.3 ± 62.6 nmol/L ($n = 12$), their median age at the start of treatment was 11 days (range = 7–66; $n = 16$), and their mean starting dose was 10.6 ± 1.6 mcg/kg levothyroxine ($n = 11$).

Controls were 19 typically developing (TD) children and adolescents (9 females; mean age = 13.3 years; age range = 9.1–16.2 years) born between August 1993 and August 2001 and selected to closely match CH in age and sex. TD controls were recruited from previous participants in the Rovet lab, current advertising in public areas of the hospital, and CH siblings ($n = 1$). Controls were excluded from participation based on prescreening (parent report) for the following criteria: drug or alcohol exposure during pregnancy, preterm birth, diagnosis of epilepsy or diabetes, history of head injury or learning disabilities, and presence of neurological, or psychological conditions.

Demographic characteristics including age at testing, sex, socioeconomic status, and Wechsler Abbreviated Scale of Intelligence (WASI) IQ of the CH and TD participants are summarized in Table 1. Family socioeconomic status (SES) was appraised using the Hollingshead scale (Hollingshead, 1975) based on the educational level and employment status of both parents. A score of 1–2 signified high SES, 3 medium SES, and 4–5, low SES. Intelligence was assessed using the two-subtest version of the WASI, based on Vocabulary and Matrix Reasoning subtests which provide an estimated full-scale IQ (FSIQ; Stano, 1999). Groups were similar in every demographic variable except estimated FSIQ which was significantly higher for TD than CH participants ($p = .025$) and differed by eight points. We chose not to treat FSIQ as a covariate in data analyses because the IQ difference is consistent with the literature and thus appears to be intrinsic to the clinical group. When a covariate is an attribute of a disorder, or is intrinsic to the condition, it is not meaningful and can be potentially misleading to "adjust" for differences in the covariate (Dennis et al., 2009).

# MEASURES

## Visuocognitive Tests

A Snellen chart was used to screen visual acuity, and all participants had normal or corrected-to-normal vision. The test battery (summarized in Table 2) included subtests from the NEPSY-Second Edition (NEPSY-II; Korkman, Kirk, &, Kemp, 2007), the WASI (Stano, 1999), the Test of Visual Perceptual Skills-revised (TVPS-R; Gardner, 1996), and the Benton Facial Recognition Test-short form (Benton, Sivan, Hamsher, Varney, & Spreen, 1983).

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**Table 2.** Neuropsychological test battery

| Domain | | Test | Description |
|---|---|---|---|
| Intellectual Ability | IQ | WASI | Estimated full-scale IQ based on Vocabulary and Matrix Reasoning subtests (Stano, 1999). |
| Attention | Visual | TEA-Ch SkySearch | Identify pairs of target stimuli amongst very similar distractors (Manly et al., 1999) |
| | Auditory | TEA-Ch Score! | Keep track of number of beeping sounds heard from audio tape (Manly et al., 1999). |
| Working Memory | Verbal | WRAML2 | Mentally reorganize list of words according to size and immediately repeat to examiner (Sheslow & Adams, 2003). |
| | Visual | TVPS-R Memory & Sequencing | Remember single abstract designs or multiple geometric shapes presented in a specific order (Martin, 2006). |
| Visuospatial | Line Orientation | NEPSY-II Arrows | Examine array of arrows arranged around a target and identify the one(s) that point to center of target (Korkman et al., 2001). |
| | Mental Rotation | NEPSY-II Geometric Puzzles | Mentally rotate and match abstract black shapes (Korkman et al., 2001). |
| Visuoconstructive | 2-D Block Design | WASI Block Design | Build (using red and white cubes) two-dimensional copies of geometric patterns (Korkman et al., 2001). |
| | 3-D Block Construction | NEPSY-II Block Construction | Build (using red blocks) three-dimensional tower constructions from two-dimensional drawings (Korkman et al., 2001). |
| Visuoperceptual | Parts-to-whole localization | NEPSY-II Picture Puzzles | Identify location of smaller segments within a larger photograph (Korkman et al., 2001). |
| | Design Matching | TVPS-R Visual Discrimination | See a target design and point to a matching design among five similar choices arranged underneath the target (Martin, 2006). |
| | Form Discrimination | TVPS-R Spatial Relationships | From a series of nearly identical designs, choose the one design that differs from four others in some detail (Martin, 2006). |
| | Visual Constancy | TVPS-R Form Constancy | Match a target design to one of four alternatives—may be larger, smaller, or differently oriented (Martin, 2006). |
| | Figure-Ground Segregation | TVPS-R Visual Figure-Ground | Match designs embedded in complex backgrounds (Martin, 2006). |
| | Design Closure | TVPS-R Visual Closure | Match a completed target to one of four fragmented designs (Martin, 2006). |
| | Face Discrimination | Benton Facial Recognition Test | Match unfamiliar faces shown in front-view, $\frac{3}{4}$ profile, or under different lighting conditions (Benton et al., 1983) |

Tests of visuospatial abilities included judgment of line orientation (NEPSY-II Arrows) and mental rotation and matching of abstract shapes (NEPSY-II Geometric Puzzles). Tests of visuoconstructive abilities included block construction in two-dimensional (WASI Block Design) and three-dimensional (NEPSY-II Block Construction) configurations. Tests of visuoperceptual abilities included localization of smaller segments within a larger photograph (parts-to-whole localization; NEPSY-II Picture Puzzles), design matching (TVPS-R Visual Discrimination), feature discrimination (TVPS-R Spatial Relationships), visual constancy (TVPS-R Form Constancy), figure-ground segregation (TVPS-R Visual Figure-Ground), design closure (TVPS-R Visual Closure), and face matching (Benton Facial Recognition Test-short form). The Benton presents faces under three viewing conditions: (1) Front-view: match faces facing forward; (2) $\frac{3}{4}$ profile-view: match front-view faces to $\frac{3}{4}$ profile-views; and (3) Lighting-view: match front-view to faces under different lighting conditions. Each correctly identified face matching the target was scored as 1 and incorrectly identified distracters were scored as 0. The maximum possible score if all faces were identified correctly is 27: 6 points for Front-view, 12 for $\frac{3}{4}$ profile-view, and 9 for Lighting-view.

For each subtest, age-normed scaled scores (mean of 10 and standard deviation of 3) were computed. The only exception was the Benton, for which no child norms are available and raw scores were used to compare group performance.

## Ecologically Valid Test of Visuospatial Ability

Participants were asked to rate their own sense of direction using a self-report questionnaire, which assesses one's ability to orient themselves in space. Participants completed a child-friendly version of the SBSDS (Hegarty et al., 2002) which

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contains fifteen Likert-type items. The original SBSDS was reworded such that the core content was maintained but was made appropriate for the reading level and spatial interactions of children (e.g., instead of "I have a poor memory for where I left things" an item read "I often forget where I left things"). All items were scored such that a higher rating indicated a poorer self-reported sense of direction. An average score was computed for the 15 questions.

Hegarty and colleagues (2002) have shown that the SBSDS is internally consistent, valid, and has good test–retest reliability. Validity studies in adults show that the SBSDS is: (1) related to tasks that require updating location in space as a result of self-motion, (2) more highly correlated with tests of spatial knowledge that involve orienting oneself within the environment than with tests that involve estimating distances or drawing maps, and (3) more highly correlated with measures of spatial knowledge acquired from direct experience in the environment than with measures of knowledge acquired from maps, video, or virtual environments.

## Tests of Attention and Working Memory

Attention was assessed using the SkySearch and Score! subtests of the Test of Everyday Attention for Children (TEA-Ch, Manly, Robertson, Anderson, & Nimmo-Smith, 1999). Working memory was assessed with the Verbal Working Memory subtest of the Wide Range Assessment of Memory and Learning – 2nd edition (WRAML2; Sheslow & Adams, 2003) and the Test of Visual Perceptual Skills-revised (TVPS-R; Gardner, 1996). Details are provided in Table 2.

## Early TH Status

To characterize the degree of TH insufficiency in CH, and thus the effects of the early TH deficiency on visual function, the following data were collected from each child's medical record: disease etiology (athyrosis vs. ectopia vs. dyshormonogenesis); TSH level at screening; T4 and TSH levels at diagnosis; age at diagnosis and start of treatment; and initial levothyroxine dose.

## Current TH Status

Small blood samples were collected from consenting participants between 2:30 and 3:30 p.m. on the day of testing to control for diurnal variations in TH levels. This took place after each participant completed the clinical and behavioral tests. They were either taken to the bloodwork clinic or a nurse visited our laboratory. All participants were provided with an EMLA patch, a topical anesthetic, before blood samples were taken. The patches were not mandatory, but could be used if desired. Samples were assayed centrally for TSH and free thyroxine (fT4).

Of the 19 CH cases, 12 consented to donating a blood sample after neuropsychological and experimental testing (7 males; mean age = 12.7 years; age range = 9.1–15.7 years). Of the 19 TD controls, 13 consented to donating a blood sample on the day of testing (6 males; mean age = 13.7 years; age range = 10.8–15.7 years). CH who did and did not provide a blood sample on the day of testing did not differ in age ($F<.001$; $p = .985$), sex ($\chi^2 = .425$; $p = .650$), or SES ($F = .279$; $p = .604$). Similarly, there were no significant differences between TD who did and did not provide a blood sample in terms of their age ($F = .853$; $p = .362$), sex ($\chi^2 = .442$; $p = .709$), or SES ($F = 2.301$; $p = .139$). Thus, concurrent TH data from the CH and TD samples are thought to be representative of each population.

In CH, the median TSH was $2.46 \pm 3.72$ mU/L, which is within the normal reference range of 0.5–5.0 mU/L, and the mean fT4 was $21.1 \pm 3.06$ pmol/L, which is within the reference range of 10.0–23.0 pmol/L. In TD, the median TSH was $1.29 \pm 1.05$ mU/L, which is within the normal reference range of 0.5–5.0 mU/L, and the mean fT4 was $17.3 \pm 2.66$ pmol/L, which is within the reference range of 10.0–23.0 pmol/L.

## Statistical Analyses

Data were first analyzed for outliers based on visual inspection of boxplot data from SPSS 21.0, where outliers are defined as cases with values 1.5 times the interquartile range from the upper and lower edges of the box. A different TD outlier was found in each of NEPSY-II Arrows, WASI Block Design, TVPS-R Visual Discrimination, and TVPS-R Visual Closure, and one CH outlier was found for NEPSY-II Geometric Puzzles. Another CH did not complete the Benton Facial Recognition test. One CH did not complete the attention and working memory tests; one additional CH and four TD had verbal working memory tests that were spoiled because of administration error. Outliers were winsorized to the 10th or 90th percentile and missing values were imputed/replaced with group means according to the methods of Donders and colleagues (Donders, van der Heijden, Stijnen, & Moons, 2006). Data were then analyzed for normality using the Shapiro-Wilk test; because data were not normally distributed, visual outcome data were submitted to an aligned rank transformation, to facilitate a non-parametric factorial analysis (Wobbrock, Findlater, Gergle, & Higgins, 2011). Transformed visual outcome data were analyzed using group membership as a between-subjects factor in a multivariate analysis of variance (MANOVA), which controls for multiple comparisons. Clinical significance was assessed by classifying each participant's score as either falling within or outside the clinically significant range, defined as a scaled score $\leq 6$, computing the proportion of each group that falls within that range, and using $\chi^2$ analyses to compare the two groups.

Given the small sample size and lack of normality in the data, non-parametric Spearman correlations were used to assess the relationship between: (1) direct visuocognitive and self-report measures, and (2) visuocognitive measures and both early and current TH levels. Significance testing was two-tailed with $\alpha$ of 0.05.

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**Table 3.** Visuocognitive test results

| | | CH | | TD | |
|---|---|---|---|---|---|
| Domain | Measure | Median | Interquartile Range | Median | Interquartile Range |
| Visuospatial | NEPSY-II Arrows* | 10.0 | 9.0–12.0 | 12.0 | 11.0–13.0 |
| | NEPSY-II Geometric Puzzles | 10.0 | 7.8–11.0 | 10.0 | 9.0–14.0 |
| Visuoconstructive | WASI Block Design | 12.0 | 9.0–13.0 | 11.0 | 11.0–14.0 |
| | NEPSY-II Block Construction* | 11.0 | 8.0–12.0 | 12.0 | 10.0–12.0 |
| Visuoperceptual | NEPSY-II Picture Puzzles** | 9.0 | 6.0–11.0 | 10.0 | 10.0–14.0 |
| | TVPS-R Spatial Relationships | 14.0 | 11.0–15.0 | 12.0 | 11.0–15.0 |
| | TVPS-R Visual Discrimination* | 10.0 | 8.0–12.0 | 13.0 | 10.8–15.0 |
| | TVPS-R Form Constancy | 11.0 | 4.0–12.0 | 11.0 | 9.0–16.0 |
| | TVPS-R Visual Figure-Ground | 12.0 | 8.0–15.0 | 13.0 | 11.0–18.0 |
| | TVPS-R Visual Closure | 11.0 | 6.0–12.0 | 12.0 | 9.5–13.3 |
| | Benton Facial Recognition Test* | 43.0 | 38.5–49.0 | 47.0 | 43.0–49.0 |

*Note*. $^{**}p < .05$, $^{*}p < .10$.

## RESULTS

### Visuocognitive Test Results

MANOVA revealed significant group differences in visuocognitive outcome $F(11,26) = 3.311$, $p = .006$, $\eta^2 = .583$. Univariate tests were significant with medium to large effect sizes for NEPSY-II Block Construction $F(1,36) = 4.133$, $p = .049$, $\eta^2 = .103$, $d = .68$, NEPSY-II Picture Puzzles $F(1,36) = 5.998$, $p = .019$, $\eta^2 = .143$, $d = .82$, and Benton Facial Recognition $F(1,36) = 5.942$, $p = .020$, $\eta^2 = .142$, $d = .81$, and demonstrated a trend for NEPSY-II Arrows $F(1,36) = 3.863$, $p = .057$, $\eta^2 = .097$, $d = .66$ and TVPS-R Visual Discrimination $F(1,36) = 2.114$, $p = .086$, $\eta^2 = .080$, $d = .48$, with CH scoring below TD in all instances (see Table 3). Groups did not differ on any other visual outcome measure. Six out of 18 CH and no TD scored in the clinically significant range on NEPSY-II Picture Puzzles ($\chi^2 = 7.559$; $p = .008$), suggesting significant problems for participants with CH on this subtest. Groups did not differ in clinical significance on any other test. Follow-up analysis of the three viewing conditions in the Benton task showed that CH were significantly outperformed by TD on the $\frac{3}{4}$ profile-view condition ($U = 69.5$; $r = .49$) but did not differ in either the Front-view ($U = 124.0$; $r = .20$) or Lighting-view ($U = 126.0$; $r = .26$) conditions. MANOVA revealed no group differences in attention/working memory $F(5,32) = 0.357$; $p = .874$, $\eta^2 = .053$ (Table 4).

### Self-reported Sense of Direction

Data from the child-modified SBSDS were normally distributed; as such the data were analyzed with the parametric ANOVA test. One CH did not complete this test. Results showed significant group differences ($F = 5.359$; $\eta^2 = .133$; $p = .027$) with the CH group reporting a poorer sense of direction (mean = 3.03; $SD = 0.48$) than the TD group (mean = 2.66; $SD = 0.49$).

There were no significant correlations between SBSDS and any visuocognitive test in either the TD or CH groups.

### Early TH Status

Etiological subgroups did not differ on visuocognitive outcome measures using the Kruskal-Wallis test. Analysis of TH levels at screening and diagnosis showed that higher screening TSH, signifying more severe hypothyroidism, was associated with lower TVPS-R Spatial Relations scores ($r_s = -.719$; $p = .019$; $n = 10$) and that higher TSH at diagnosis was correlated with lower NEPSY-II Block Construction ($r_s = -.569$; $p = .027$; $n = 15$). Contrary to expectation, lower T4 values at diagnosis, signifying more severe hypothyroidism,

**Table 4.** Attention and working memory results

| | | CH | | TD | |
|---|---|---|---|---|---|
| Domain | Measure | Median | Interquartile Range | Median | Interquartile Range |
| Visual Attention | TEA-Ch Sky Search | 10.5 | 8.0–13.0 | 11.0 | 10.0–13.0 |
| Auditory Attention | TEA-Ch Score! | 10.0 | 7.0–11.25 | 11.0 | 8.0–12.0 |
| Verbal Working Memory | WRAML2 Verbal Working Memory | 10.0 | 8.0–11.0 | 11.0 | 10.0–13.0 |
| Visual Working Memory | TVPS-R Memory | 9.0 | 8.0–12.0 | 10.0 | 9.0–12.0 |
| Visuospatial Working Memory | TVPS-R Sequencing | 10.0 | 8.0–11.0 | 9.0 | 7.0–12.0 |

*Note*. There were no significant group differences.

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were associated with better TVPS-R Closure scores ($r_s = -.585$; $p = .046$; $n = 12$). No significant correlations were seen between treatment factors and visuocognitive function.

### Current TH Status

In the CH group, higher TSH on the day of testing was correlated with lower NEPSY-II Block Construction ($r_s = -.608$; $p = .036$).

In the TD controls there were no significant correlations between current TH levels and any visuocognitive measure.

## DISCUSSION

Congenital hypothyroidism (CH) is associated with persisting cognitive problems, amongst which visuocognitive problems are the most significantly affected (Rovet, 1999a). We investigated several unresolved questions about the nature and range of visuocognitive abilities affected by early TH insufficiency in a single CH cohort. We found selective but not global deficits; affected were some visuospatial processes (judging line orientation but not mental rotation), some visuoconstructive processes (constructing three-dimensional block towers but not two-dimensional block designs), and some visuoperceputal processes (localizing smaller segments within a larger photograph and design matching but not feature discrimination, visual closure, or figure-ground segregation). New information from the study is that tested weaknesses were accompanied by ecological problems in self-reports of direction sense and navigation, showing that children with CH not only have visuocognitive difficulties on laboratory testing, but in their everyday lives.

This is the first study to examine the three categories of visuocognitive abilities in CH. In particular, visuoperceptual processes have been understudied. We have shown that the majority of visuoperceptual abilities are not affected by early TH insufficiency. CH were comparable to TD peers at discriminating small features of designs, recognizing objects as they changed size/shape/orientation, distinguishing an object from a complex background, and recognizing a complete object from fragmented information. Notable exceptions were for the ability to localize smaller segments within a larger photograph and to discriminate and match designs (TVPS-R Visual Discrimination). The TVPS-R Visual Discrimination subtest differs from the rest of the TVPS-R tests in that it requires intact integration of local features into perceptual wholes; Spatial Relationships, on the other hand for example, can be performed successfully by local processing of select features. The observed group differences in Visual Discrimination, Picture Puzzles, and Block Construction suggest that parts-to-whole integration underlies many of the visuocognitive difficulties for CH.

An inability to integrate parts of a design into a coherent whole may explain another visuoperceptual deficit we observed in CH, in face perception: CH had no problems matching unfamiliar faces that were presented in straight-on/front-view or under different lighting conditions. Given that $\frac{3}{4}$ profile-view faces are thought to promote better recognition memory for previously unfamiliar faces than do full-face views (Bruce, Valentine, & Baddeley, 1987), we expected CH to be better at matching $\frac{3}{4}$ profile-view than front-view faces; however they had difficulty matching $\frac{3}{4}$ profile-view faces. A possible explanation for this finding is that the act of mentally rotating the $\frac{3}{4}$ profile-view face before matching it to the front-view conferred a disadvantage to this group. However, as a group, CH did not have trouble mentally rotating and matching abstract shapes (NEPSY-II Geometric Puzzles). An alternative explanation is that it may be more difficult to extract holistic face representations when faces are presented in $\frac{3}{4}$ profile- versus straight-view. Given that CH have difficulty with parts-to-whole processing it may be that weakness in this visuocognitive ability underlies their difficulty matching $\frac{3}{4}$ profile-view faces.

Of interest, results from direct testing of visuospatial ability did not correlate with subjective assessments of visuospatial function. We failed to observe any significant correlations between overall scores on the SBSDS and any of the direct measures of visuospatial processing in either CH or typically developing children and adolescents. There are a few possible explanations for this lack of relationship: either the psychological tests fail to tap into an ecologically valid spatial ability, or CH are inaccurate at judging their own spatial abilities. The scale's authors also failed to find a correlation between the self-reported SBSDS and their neuropsychological tests of visuospatial ability (Hegarty, Montello, Richardson, Ishikawa, & Lovelace, 2006). They did however find that self-reported sense of direction correlated with the ability to learn the layout of a large environment (Hegarty et al., 2006). Thus, the likely explanation for our findings is that standardized neuropsychological tests measure a different spatial ability than does the ecologically valid scale. Of important note for neuropsychologists is the independence of real-world and tested visuospatial abilities. It cannot be taken for granted that poor psychological performance translates to poor performance in the real world; or vice versa that intact performance during neuropsychological testing translates to intact real world performance.

A secondary aim of this study was to examine whether the pattern of visuocognitive results could be ascribed to domain-general abilities like attention or working memory. Importantly, groups did not differ on any visual or auditory test of attention or working memory suggesting that these abilities are intact in CH. These findings suggest that the visual dysfunction in CH is not directly attributable to problems with attention or working memory.

Although this investigation of higher-order visual function in CH provides novel information and parcellation of the visuocognitive deficits associated with early TH insufficiency, there are several limitations to our findings. First, our sample is relatively small. However, the relatively low prevalence of CH makes it difficult to recruit large sets of participants within a restricted age range. While the current use of closely age- and sex-matched controls may have circumvented this problem to a small degree, nevertheless

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more data with a larger sample should be collected. Second, there is an equal proportion of females and males in our CH sample, despite the fact that the disorder occurs more often in girls than boys (generally with a ratio of 2:1, Lorey & Cunningham, 1992). However, there were no significant differences between the two sexes on any visual outcome measure suggesting that sex is not a factor in these findings. Third, even though neuropsychologists agree on a division of visual tests into the three categories presented here, the tests themselves are not "pure" measures of visuospatial, visuoconstructive, and visuoperceptual ability and often these abilities are confounded in a single test. For example, the NEPSY-II Geometric Puzzles task confounds mental rotation (visuospatial ability) with object identification (visuoperceptual ability). Poor performance on this task could be driven by a weakness in either ability. This underscores the need for experimental paradigms that more stringently control for and isolate the desired visual abilities. Next, although the SBSDS has been validated for use with adults, this is the first study to use it with children and adolescents. While we believe the use of this self-report measure of visuospatial ability is a strength of this study, we acknowledge that it has yet to be validated for use with this population. Nevertheless, all participants appeared to understand each of the items in the SBSDS. Finally, the lack of equivalence between CH and TD in terms of FSIQ may be construed as a limitation in that it is possible that higher IQ contributes to better performance on visuocognitive tasks in the TD group. However, the IQ difference seems to be driven by the verbal skills score (Vocabulary) as opposed to the visual-spatial reasoning score (Matrix Reasoning) thus suggesting that IQ is not contributing to the observed group differences on visuocognitive testing.

The data add new information about TH status, which was associated with one of the affected functions, namely three-dimensional block construction. We observed that TH levels differentially affect different visuocognitive processes. This variability likely stems from one or a combination of the following: (1) the timing and extent of TH deficiency, (2) the extent of TH dependence within different structures subserving visual cognition over the course of brain development, or (3) the sensitivity of underlying brain structures to variations in TH availability. Specifically, we observed that higher TSH both at diagnosis and concurrently, signaling lower circulating levels of bioactive TH available to the brain, was associated with lower NEPSY-II Block Construction scores. This observation suggests that early TH insufficiency and persisting hypothyroidism both have deleterious effects on visuocognitive function. However, the mechanism of the early and concurrent TH effects on visuospatial abilities are likely different. How can TH have both organizational effects on the developing brain as well as activational effects on the mature brain? Dratman and Gordon (1996) proposed that it is a matter of ontogenic timing: TH regulates neurodevelopment early in ontogenesis before neurotransmitter apparatus is in place and as these apparatuses come into place, TH's role as a neurotransmitter comes to the fore. Thus, in the developing brain TH acts as a growth regulator directing neural organization, but in the adult brain it acts as a neurotransmitter, modulating various cognitive processes. The activational effects of ambient TH on cognitive function are likely due to its interactions with neurotransmitter systems, including dopamine (Haugen, 2009) and norepinephrine (Mano et al., 1998). Of interest, in contrast to the Leneman et al (2001) findings, we see that disease etiology, reflecting severity of prenatal TH insufficiency, is unrelated to the visual outcomes measured in this particular cohort. We interpret this to suggest that visuocognitive outcome is vulnerable to even the mildest forms of CH.

## CONCLUSION

It may be that visuoconstructive processes required to put together parts to form a single whole underlie many of the visuocognitive difficulties experienced by CH. Importantly, the visuospatial deficits extend to reported problems in spatially orienting themselves in their environment, although the abilities measured by standardized neuropsychological tests are likely different from the spatial skills required for good sense of direction.

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