Hippocampal Size and Memory Functioning in Children and Adolescents with Congenital Hypothyroidism

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Background: Despite early diagnosis and treatment of congenital hypothyroidism (CH) after newborn screening, selective and persistent neurocognitive weaknesses may be seen. One area of particular weakness is memory, especially on tasks known to be mediated by the hippocampus. However, the hippocampus has not been directly studied in this population.

Objective: Our objective was to use magnetic resonance imaging to determine whether children and adolescents with CH have reduced hippocampal size and abnormal hippocampal growth patterns relative to peers and whether reduced hippocampal volumes in CH predict poor memory performance.

Methods: Studied were 35 CH and 44 typically developing controls aged 9–15 yr. All were assessed using standardized tests of intelligence and verbal and visual memory and received an magnetic resonance imaging scan. Parents completed a questionnaire of their everyday memory functioning (EMF). Right and left hippocampal volumes were measured by manual tracing.

Results: CH subjects scored significantly below controls on indices of verbal but not visual memory as well as aspects of EMF. CH subjects also had smaller hippocampal volumes, particularly on the left side. Unlike controls, who showed a positive relationship between age and hippocampal volumes, age was unrelated to hippocampal size in CH. Structure-function correlations revealed significant relationships between hippocampal volumes and EMF in controls and modest correlations between hippocampal volumes and memory test scores but not EMF in CH.

Conclusions: Compromised hippocampal development in CH may contribute to some of the memory weaknesses observed in this population. **(*J Clin Endocrinol Metab* 96: E1427–E1434, 2011)**

The hippocampus, which is essential for learning and memory (1), needs an adequate supply of thyroid hormone (TH) during development (2). Based on studies of TH-deprived rodents, an important time of need for TH during hippocampal development is from early gestation to the end of infancy (3). Indeed, such studies have shown severe learning and memory impairments (4–6) as well as reduced size of selective hippocampal subregions (*e.g.* CA1 and dentate gyrus) (7–9) and atypical hippocampal functioning (10).

In several human conditions involving an early lack of TH, weak learning and memory skills are also seen (11, 12). For example, patients with congenital hypothyroidism (CH) treated early in life after newborn screening are outperformed by their peers and siblings on various neuropsychological tasks (13), including measures of learning

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Abbreviations: CH, Congenital hypothyroidism; MRI, magnetic resonance imaging; TH, thyroid hormone.

and memory (14). Although the performance of these patients falls within the normal range, their scores are significantly below controls on word-pair and object-location recall tasks (15), which are often compromised after hippocampal damage (16). In contrast, no group differences are seen on face recognition and working memory tasks, which are known to be sensitive to structures other than the hippocampus (17). However, the hippocampus has not been directly studied in children with CH.

As part of a larger study on the role of TH in the hippocampus and memory, we performed magnetic resonance imaging (MRI) scanning on children and adolescents with CH as well as similar-age typically developing peers as controls. The primary aims were to determine whether groups differed in size of their hippocampi and hippocampal growth patterns and to examine whether their memory skills were correlated with hippocampal size. It was hypothesized that children with CH would show smaller hippocampi and different hippocampal growth patterns than controls and that those CH children with smaller hippocampi would demonstrate weaker memory performance.

Subjects and Methods

Participants

Participants were derived from two studies with mostly similar task requirements, an initial pilot study (February 2005 to November 2006) and a larger funded study (October 2007 to December 2010) examining multiple memory abilities and using both structural and functional MRI techniques. The total sample consisted of 79 participants aged 8.7–14.9 yr (see Table 1), 35 with CH (14 male, 21 female) and 44 typically developing controls (19 male, 25 female). Fourteen CH subjects and 16 controls were participants in the first study, and 21 CH subjects and 28 controls were from the second study.

The CH group consisted of past participants (n = 25) or new recruits from the Endocrine Clinic at The Hospital for Sick Children (SickKids) (n = 10). Of the past participants, 11 born from 1993–1995 were recruited from an earlier memory study (18), and 14 born from 1996–2001 belonged to a cohort followed since birth. All children except two were detected through the Ontario newborn screening program, which identifies CH based on an elevated TSH value. The exceptions were a male whose newborn screening sample was lost and who was clinically diagnosed at 62 d of age and a male born outside of Canada and diagnosed at 30 d of age. The CH group consisted of 11 children with thyroid agenesis, 16 with ectopic glands, and six with dyshormonogenesis. Two children had unknown etiologies because the parents of one refused the technetium scan at SickKids and the other was born afar. Information ascertained from children's medical charts revealed a median screening TSH of 155 mU/liter (range, 20–940; n = 32), mean ± SD total and free T_4 at diagnosis of 51 ± 39.5 nmol/liter (n = 26) and 8.3 ± 5.8 (n = 14), and a median TSH of 195 mU/liter (range, 15–1000; n = 17) at diagnosis. All children except five began treatment before 18 d of age (median = 13 d); the latter included four with dyshormonogenesis and equivocal newborn screening results who were followed only until their T_4 levels declined, and then they commenced treatment, and the child missed by the newborn screening program (see above). The median starting dose by weight was 10.7 μg/kg (range = 5.9–16.3 μg/kg). All children but one with dyshormonogenesis whose T_4 values were in the normal range at diagnosis received a starting dose above 8.0 μg/kg.

Controls were also derived from several sources: 34 past participants either belonged to a longitudinal cohort followed since birth (n = 21) or were newly recruited via postings in the hospital (n = 10). Only children with IQ between 70 and 130 were included. Excluded were children having a medical disorder affecting brain development or brain function, a learning disability, or a psychiatric disorder. Also excluded were children with antenatal exposure to alcohol or other teratogens or born preterm.

To be included presently, no child in either group could have contraindications to MRI from braces or other implanted metal devices.

Procedures

After written consent by parents and verbal assent by participants, the children underwent a 3- to 4-h neuropsychological assessment that included a brief intelligence test and tests of verbal and visual memory while parents completed several questionnaires. Immediately after the assessment, all children underwent a 1-h scan in a 1.5-T General Electric Excite Twin Speed scanner (Milwaukee, WI) in the Diagnostic Imaging Unit at SickKids. During structural scanning, they viewed movies or cartoons via MR-compatible goggles. The 7-min scan that was the basis for the current analysis was acquired near the beginning of the MRI session, typically at about 5 min. Depending on the particular study, the remainder of the hour was spent obtaining either additional structural MRI scanning or conducting functional MRI studies. Use of goggles was generally quite effective in reducing motion artifacts. During acquisition, scans were inspected and, if in the opinion of the radiologist were too blurry, they were redone. Only clear scans were used.

Upon session completion, each participant received a movie pass, certificate of participation, letter for high school volunteer hours (if applicable), and a CD containing pictures of his or her own brain. Parents were compensated for transportation costs and within 2 months of the assessment received a report describing their child's cognitive abilities. A neuroradiologist masked to group status examined MRI images qualitatively for indication of abnormalities, and the child's pediatrician was informed of any abnormalities. All procedures were approved by the Research Ethics Board at SickKids.

Tests and measures

Intelligence was assessed using the two-subtest version of the Wechsler Abbreviated Scale of Intelligence, which included Vocabulary and Matrix Reasoning subtests (19). Verbal memory was assessed with the Children's Memory Scale Stories subtest (20), which required participants to listen to two stories read by the examiner and, after each, immediately recall the story's contents (Immediate Recall). After a 30-min delay (Delayed Recall), they were asked to recite both stories from memory and after this, answer 20 yes/no questions assessing recognition of story facts (Delayed Recognition). All scores were converted to age-normed

scale scores (mean = 10; SD = 3) with a higher score signifying better performance. Visuospatial memory was assessed with the Rey-Osterrieth Complex Figure task, which required participants to copy a complex figure and then redraw it from memory after a 30-min delay (21). A 36-point scale was used to score drawing accuracy.

Parents completed a questionnaire seeking information on demographics, pregnancy, medical history, early development, school status, and family medical and psychological history. They also completed the Everyday Memory Questionnaire (22) requiring them to rate using a nine-point scale (1 = not at all in the last 3 months; 9 = more than once a day) how their child behaved in 28 everyday memory situations (*e.g.* forgets where he/she puts something, forgets to do things he/she said would do). This questionnaire yields a total memory score and five individual factor scores: Retrieval, Task Monitoring, Conversational Memory, Spatial Memory, and Memory for Activities (23). Higher scores on this task signify worse everyday memory functioning.

Image acquisition and processing

Images were acquired using different protocols for the two studies: a gradient-echo T1-weighted series (TR = 24 msec; TE = 5 msec; flip angle = 45°; field of view of 24 cm, slice thickness of 1 mm, and no gap) for the first study and a fast gradient-echo T1-weighted series (TR = 10.372 msec; TE = 4.264 msec; flip angle = 20°; field of view of 24 cm, slice thickness of 2 mm reconstructed at 1 mm, and no gap) for the second.

Structural images were processed using ANALYZE version 6.0 software. First, brain images were extracted from the skull and cerebral spinal fluid. Next, the extracted brain was normalized in standard space using anterior and posterior commissure alignment. One image analyst determined the total intracranial volumes. Left and right hippocampal volumes were manually traced by two image analysts masked to group status who each used a trackball-driven cursor to manually trace all hippocampi on a slice-by-slice basis (Fig. 1). Traced regions included the dentate gyrus, hippocampus proper, and subicular complex (24). On all slices, analysts outlined each hippocampus in the coronal plane beginning at the rostral (anterior) end when the hippocampal head first appeared below the amygdala and ending when the crura of the fornix departed from the hippocampal tail at the caudal end. Sagittal images were also used for boundary verification to ensure the inferior hippocampal boundary was delineated from white matter and parahippocampal gyrus. Approximately 80 slices per hippocampus were individually traced for each participant. Interrater reliabilities were 98.1% for left hippocampal volumes (Cronbach $\alpha = 0.99$) and 99.8% for right hippocampal volumes (Cronbach $\alpha = 1.00$).

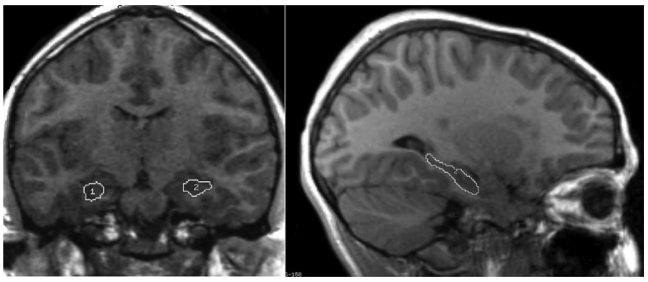

FIG. 1. Coronal (at slice 122) and sagittal (at slice 158) views of hippocampal tracings using ANALYZE version 6.0 software. The left hippocampus is labeled as object 1, and right hippocampus is labeled as object 2 (neurological view).

TABLE 1. Demographic characteristics of CH and control groups

	CH (n = 35)	Control (n = 44)
Gender (% male)	40	57
Age (yr)[a]	12.1 ± 1.7	11.6 ± 1.5
Full-scale IQ[a]	105.6 ± 9.7	114.8 ± 8.3

[a] Results expressed as mean ± SD.

Statistical analyses

For the few cases with unacceptable scans, MRI data were replaced with the mean measurements of children in the same group, same gender, and same age range. All analyses were conducted in SPSS version 17. Demographic data were analyzed using *t* tests and χ^2 tests, whereas memory results were analyzed using *t* tests with the Bonferroni *P* correction applied within tests. Everyday Memory Questionnaire Total scores were compared using a *t* test and factor scores using multivariate ANOVA. Intracranial volumes were compared via a *t* test, whereas hippocampal volumes were compared using analysis of covariance with intracranial volumes and age as covariates and side as an independent factor. In these analyses, the *P* value was set at 0.05 while $P < 0.10$ was considered a trend. Pearson correlations served to correlate hippocampal measurements and memory results with the *P* value set at 0.01 to compensate for multiple correlations; $P < 0.05$ value was considered a trend.

Results

Table 1, which provides demographic data, shows groups had similar gender compositions and ages. The CH group scored significantly ($P < 0.001$) below controls in IQ, but because this is a defining feature of the CH profile (25), it was not considered a relevant covariate (26).

Table 2, containing the memory test and questionnaire data, shows the CH group scored below controls on most indices. On the Children's Memory Scale, groups differed significantly on the Stories Immediate ($P = 0.01$) and Delayed Recall ($P = 0.02$) conditions and showed a trend for Delayed Recognition ($P = 0.06$). On the parent-completed Everyday Memory Questionnaire, CH children reportedly had more overall everyday memory problems ($P = 0.04$) than controls, particularly regarding their spatial memory ($P = 0.04$). Groups did not differ on copying or recall scores of the Rey-Osterreith Complex Figure.

Table 3 provides the intracranial and hippocampal volume data. CH and controls did not differ in intracranial volumes. Multivariate analysis of covariance with age and intracranial volume as covariates revealed a significant group difference for the left hippocampal volume ($P = 0.02$), reflecting the smaller hippocampi of the CH group.

TABLE 2. Mean ± standard deviation results on memory test indices for CH and Control groups

Test	Scale/subtest	CH (n = 35)	Control (n = 44)	*P* value
Children's Memory Scale Stories[a]	Immediate	10.7 ± 2.6	12.2 ± 2.5	0.01
	Delayed	11.0 ± 2.8	12.5 ± 2.8	0.02
	Delayed Recognition	10.5 ± 3.1	11.9 ± 3.1	0.06
Rey Osterrieth Complex Figure[b]	Copy	28.5 ± 5.4	28.3 ± 6.5	0.87
	Delayed Recall	17.6 ± 8.1	18.0 ± 7.2	0.82
Everyday Memory Questionnaire[b]	Retrieval	14.7 ± 7.8	11.9 ± 6.3	0.10
	Task Monitoring	11.4 ± 6.5	9.5 ± 2.4	0.08
	Conversational Memory	11.0 ± 5.9	9.1 ± 3.8	0.07
	Spatial Memory	7.5 ± 5.4	5.5 ± 2.5	0.04
	Memory for Activities	14.8 ± 7.6	12.4 ± 4.6	0.09
	Total	59.2 ± 25.9	48.4 ± 15.8	0.04

[a] Expressed as scale scores (mean = 10; SD = 3).

[b] Expressed as raw scores.

Although groups did not differ significantly in their right hippocampal volumes, CH had smaller volumes at a trend level ($P = 0.10$). In both groups, left hippocampi were smaller than right, and this laterality difference was significant at a trend level ($P = 0.06$), consistent with the extant literature on typically developing youth (27). There were no gender differences in hippocampal volumes.

To examine age-related changes in hippocampal size, separate correlations between chronological age and right and left hippocampal volumes were computed for both groups (see Fig. 2). For controls, significant correlations were observed between age and both left and right hippocampal volumes ($r = 0.515$, $P < 0.01$; $r = 0.315$, $P < 0.05$). However, in CH, age was unrelated to hippocampal volumes (left: $r = 0.265$; right: $r = 0.121$, $P > 0.05$ for both), and this finding was maintained even when intracranial volume was entered as a covariate. In addition, hippocampal size was not correlated with early TH levels, age at starting treatment, or starting dosage in CH, and the different etiological CH subgroups did not differ in their hippocampal size.

Finally, to examine the relationships between hippocampal size and memory, partial correlations were computed between memory test scores and hippocampal volumes for each group using age and intracranial volume as covariates. Results showed different patterns of relationships for controls than CH. In controls, right hippocampal volumes were significantly correlated with Everyday Memory Questionnaire Retrieval ($r = -0.354$; $P < 0.01$) and Memory for Activities ($r = -0.347$; $P < 0.01$) factor scores. Similar effects (at a trend level only) were seen between left hippocampal volumes and Everyday Memory Questionnaire Retrieval ($r = -0.247$; $P < 0.05$) and Activities scores ($r = -0.280$; $P < 0.05$). These results were not observed in the CH group, who instead showed effects at a trend level between right hippocampal volumes and Children's Memory Scale Stories Immediate Recall ($r = 0.299$; $P < 0.05$) scores and left hippocampal volumes and Rey-Osterreith Complex Figure delayed recall scores ($r = 0.302$; $P < 0.05$).

TABLE 3. Mean ± SD for intracranial and hippocampal volumes for CH and control groups

	CH (n = 35)	Control (n = 44)	*P* value
Intracranial volume[a]	1644.5 ± 18.9	1601.4 ± 19.3	NS
Right hippocampus (mm^3)	1890.4 ± 266.0	1968.4 ± 281.4	0.10
Left hippocampus (mm^3)	1858.1 ± 212.2	1942.2 ± 260.9	0.02

NS, Not significant.

[a] Expressed per 1000 mm^3.

Discussion

Present findings showed that relative to controls, children and adolescents with CH exhibit poorer recall on verbal but not visuospatial memory tasks and an increased number of everyday memory problems, especially in everyday spatial memory. The CH group also had smaller hippocampi than controls, particularly on the left side. Whereas controls showed an increase in hippocampal size over the age range studied (9–15 yr), this was not seen in the CH group. We also observed group differences in patterns of relationships between hippocampal size and aspects of memory functioning: in controls, larger hippocampal volumes were associated with better everyday memory functioning, whereas in CH, a modest relationship with better memory task performance but not better everyday memory was seen. We did not observe any associations between indices of severity of early hypothyroidism and current hippocampal volumes.

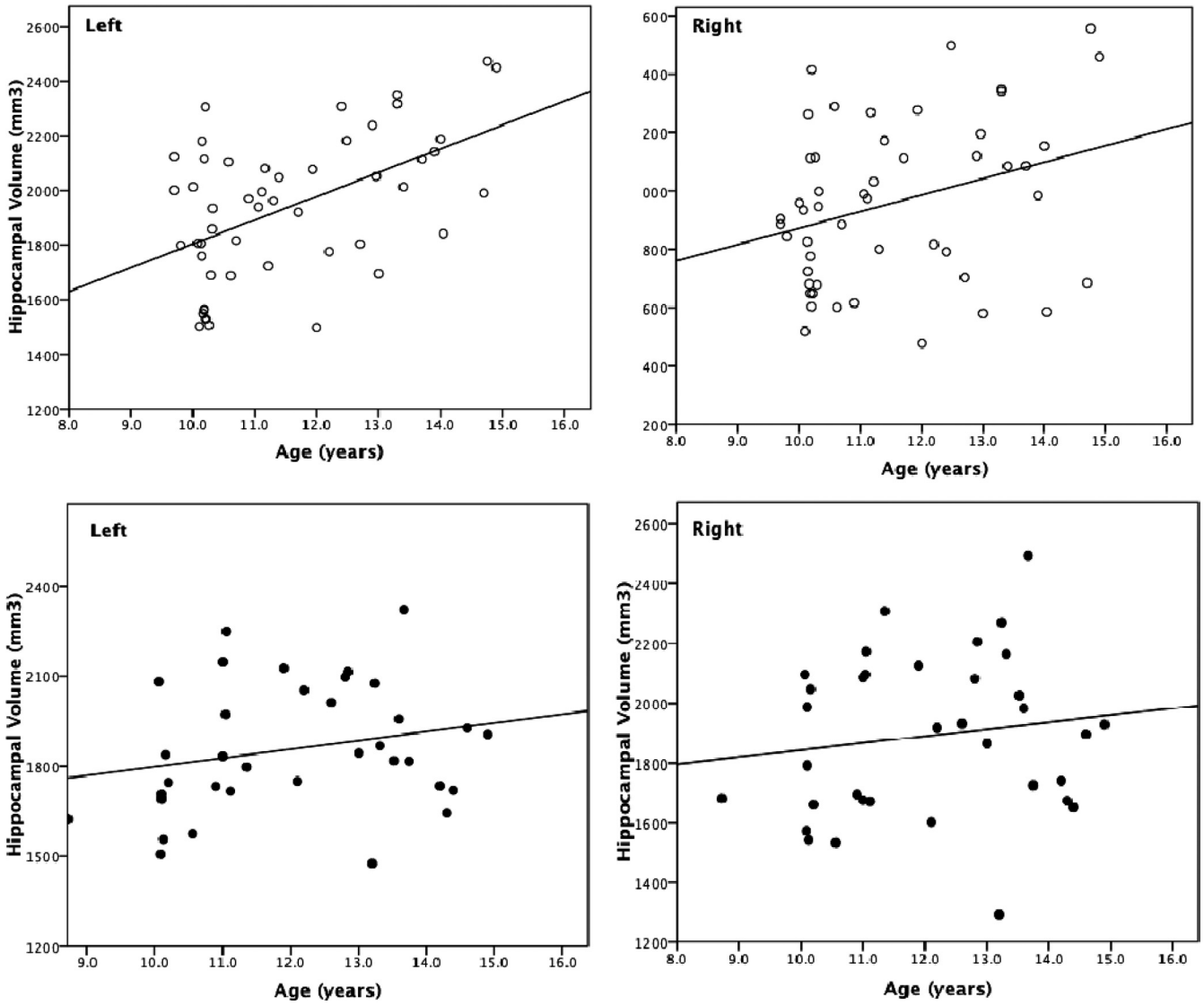

FIG. 2. Relations between age and hippocampal volumes in control (*top*, ○) and CH (*bottom*, ●) groups. In controls, right hippocampus, $y = 1435 + 46.1x$; left hippocampus, $y = 983 + 89.2x$; in CH, right hippocampus, $y = 1605 + 23.7x$ and left hippocampus, $y = 1502 + 29.6x$.

Although the CH group scored significantly below controls in general intelligence as well as verbal memory and everyday memory skills, it should be noted that the children with CH maintained scores in the average range for population norms on the particular tasks, consistent with previous reports on different cohorts of CH children (13). Although our current sample of children and adolescents with CH showed a larger difference in IQ from controls than reported previously (28), this may reflect the particular IQ instrument we used, namely the two-subtest version of the Wechsler Abbreviated Scale of Intelligence, which is comprised of just Vocabulary and Matrix Reasoning subtests. Thus, effects may be exaggerated from those when IQ tests are more comprehensive and include multiple other subtests.

In terms of memory, we observed that children with CH relative to controls showed weak verbal memory ability (Children's Memory Scale Immediate and Delayed Story recall); in contrast, groups did not differ in visuospatial memory on the Rey Osterrieth Complex Figure test. Additionally, parents reported a significantly higher degree of everyday memory problems in the CH group than controls, particularly when remembering where things are placed and how to get somewhere, suggesting real-world difficulties in visuospatial memory. The implication of these increased everyday memory functioning difficulties warrant further investigation using ecologically valid memory situation tasks to determine whether this reflects parental bias from lasting concerns about the child's medical condition or is characteristic of this population.

Importantly, present findings show that an early circumscribed loss of TH in children and adolescents with CH has a lasting impact on the hippocampus. Left hippocampal volume reductions seen in the CH group pro-

vide evidence for the first time that early TH deficiency adversely affects hippocampal development through to adolescence, and this may contribute to reduced performance on clinical memory tests. Nevertheless, the modest correlations and different patterns of relationships between hippocampal volumes and particular memory indices in CH *vs.* control groups warrants further investigation involving a larger more comprehensive battery of clinical memory tests as well as indices of memory functioning in the real world that are known to rely on the hippocampus (*e.g.* spatial navigation and prospective memory) (29, 30).

Within the CH group, correlations between clinical memory tests and hippocampal volumes reflect an association between larger left hippocampal volumes and better visuospatial memory and larger right hippocampal volumes and better verbal memory. This result is contrary to usual hippocampal functioning whereby the left hippocampus is typically associated with verbal memory (31) and the right with visuospatial memory (32). Given these correlations are quite modest, we need to exercise caution in interpreting these patterns. Nonetheless, our findings may signify that given structural abnormalities, children with CH recruit additional bilateral hippocampal resources to maintain task performance as observed in other developmental conditions (33), and by us in this cohort, using functional MRI (Wheeler, S. M., K. A. Willoughby, M. P. McAndrews, and J. F. Rovet, submitted for publication). On verbal tasks, this compensation is not sufficient because they still perform below controls. In controls, correlations with memory task performance may be absent given their hippocampi are intact, and so additional contralateral resources are not needed for them to perform adequately. It is not clear why hippocampal size and everyday memory functioning was correlated in controls only.

Interestingly, although controls showed an increase with age in both left and right hippocampal volumes reflecting a larger growth spurt on the left, this effect was strikingly absent in the CH group, at least from 9–15 yr of age. It is possible that their early lack of TH led to later disruption of developmental processes that normally occur in the hippocampus, consistent with the animal literature showing hypothyroidism early in life disrupts later processes, such as myelin formation (34). Alternatively, results also may reflect later-in-life TH fluctuations in CH because these children have their TH levels monitored only yearly in later childhood. Thus, they may be hypothyroid for periods of time before their annual check-up, including when scanned and assessed, and this may also have an impact on memory and subsequent hippocampal development.

Several limitations of the current study preclude our ability to determine the full impact of the original TH loss and its effect on the developing hippocampus. First, we lacked a precise measure of when TH levels normalized in the children and so could not determine the exact length of the hypothyroid period or its severity during this period. Likewise, we did not know when the hypothyroidism began given that only a few children in the cohort had bone age assessments at time of diagnosis. Furthermore, medical chart data were incomplete for a few cases, and therefore, the correlations between TH variables with memory abilities and hippocampal volumes did not involve the full set of cases. In addition, we did not measure TH levels at the time of assessment and scanning; ambient variations in TH are known to affect cognitive and hippocampal functioning, particularly if the individual is hypothyroid at the time, as observed in adults (14, 35, 36). Another limitation is that our finding of a relation between hippocampal volumes and age in controls but not CH was based on cross-sectional data. Clearly, longitudinal measurements of CH scans are required over the course of childhood and adolescence to determine whether the present effects reflected our cross-sectional approach. It would also be interesting to study individuals with CH at yet an older age to discern whether their lack of hippocampal growth is sustained or they make later gains with age. Furthermore, it should be noted that our findings on controls are at odds with those from the large National Institutes of Mental Health study of normal hippocampal development that reported no overall change in hippocampal volume with age (37). Nevertheless, it should be noted that this study involved a much broader age range than ours (4–25 *vs.* 9–15 yr) and that within specific hippocampal subregions (*e.g.* posterior hippocampus), quadratic trajectories with mid-age peaks were described. Close examination of these trajectories suggests an age-related increase did occur during the age interval of our controls. Notably, several other studies do report a developmental increase in this region (38–40).

Several methodological limitations also warrant discussion. To increase sample size, we presented data from consecutive studies that differed slightly in parameters used to collect the structural MRI data. However, the differences between these studies are unlikely to affect current results given that different scan parameters do not have a significant effect on structural volumes (41). In addition, any effect from the different procedures on the participants would have been identical for both CH and control groups because the two studies contained similar proportions of controls and children with CH. Finally, the structure-function relationships demonstrated presently suggest recruitment of additional hippocampal resources; however, this needs further testing using functional MRI

techniques as currently underway (Wheeler S. M., K. A. Willoughby, M. P. McAndrews, and E. D. Sheard, submitted for publication).

Overall, then, the present findings show that children and adolescents with CH have reduced memory functioning and hippocampal volumes compared with typically developing peers. Also, unlike controls, the CH group failed to show age-related increases in hippocampal volumes in the age range studied (9–15 yr). Moreover, groups differed in their patterns of relationships between hippocampal size and aspects of memory functioning. Thus, despite newborn screening and prompt treatment, early TH deficiency in CH seems to have long-lasting effects on the hippocampus and its relationship to memory functioning.

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