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Visuospatial Associative Memory and Hippocampal Functioning in Congenital Hypothyroidism

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Abstract

Congenital hypothyroidism is a pediatric endocrine disorder caused by insufficient endogenous thyroid hormone production. Children with congenital hypothyroidism have difficulties with episodic memory and abnormalities in hippocampal structure, suggesting deficient hippocampal functioning. To assess hippocampal activation in adolescents with congenital hypothyroidism ($N = 14$; age range, 11.5–14.7 years) compared with controls ($N = 15$; age range, 11.2–15.5 years), a functional magnetic resonance imaging visuospatial memory task was used. In this task, participants had to decide if object pairings were novel or were previously studied or if object pairs were in the same location as they were at study or had switched locations. Despite no group differences in task performance, adolescents with congenital hypothyroidism showed both increased magnitude of hippocampal activation relative to controls and bilateral hippocampal activation when only the left was observed in controls. Furthermore, the increased activation in the congenital hypothyroidism group was correlated with the severity of the hypothyroidism experienced early in life. These results suggest that perinatal deprivation of thyroid hormone has longstanding effects on hippocampal function and may account for memory problems experienced by adolescents with congenital hypothyroidism. (*JINS*, 2012, *18*, 49–56)

Keywords: Hippocampal formation, Congenital hypothyroidism, Thyroid hormone, Episodic memory, fMRI, Adolescents

INTRODUCTION

Congenital hypothyroidism (CH) is a pediatric endocrine disorder of newborns caused primarily by a missing, ectopic, or dysfunctional thyroid gland. This leads to an early insufficiency of thyroid hormone (TH) (LaFranchi, 1999), which is necessary for brain development. Although CH is readily treated with replacement TH, clinical diagnosis was previously delayed due to the late appearance of outward symptoms and as a result, CH was a leading cause of mental retardation. However, with the advent of newborn screening, diagnosis, and treatment of CH now take place shortly after birth thereby avoiding retardation (Dugbartey, 1998; Rovet, 1999). Nevertheless, affected children still exhibit a variety of subtle cognitive weaknesses (Rovet, 1999, 2002) that persist into adulthood (Oerbeck, Sundet, Kase, & Heyerdahl, 2005).

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One area of notable weakness among children with CH is their learning and memory abilities (Rovet, 2002), which typically fall below peers on standard neuropsychological tests, although still within the normal range of population norms (Oerbeck et al., 2005; Rovet, 1999; Rovet, Ehrlich, & Sorbara, 1992). Previous studies have shown that areas particularly affected are their verbal-associative recall and spatial learning abilities (Rovet, 1999, 2002), which are known to rely on the hippocampus. In contrast, their working memory, which involves primarily extra-hippocampal structures (Eichenbaum, 2001; Mayes, Montaldi, & Migo, 2007; Milner, Corkin, & Teuber, 1968; Vargha-Khadem, Gadian, & Watkins, 1997) is preserved (Hepworth, Pang, & Rovet, 2006; Rovet, 1999). These findings are supported by basic research with rodents deprived perinatally of TH and showed significant learning and memory impairments as well as structural and functional abnormalities of the hippocampus (Gilbert, 2004; Gilbert & Sui, 2006; Rami, Rabie, & Patel, 1986; Rami, Patel, & Rabié, 1986). Consequently, these findings led us to speculate that the memory weaknesses in children with CH may also reflect altered hippocampal

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functioning (Rovet & Daneman, 2003; Rovet, 1999, 2002; Song, Daneman, & Rovet, 2001). Recently, we reported these children show reduced hippocampal volumes and disturbed hippocampal maturation during adolescence and that their hippocampal volumes are correlated with performance on selective memory tasks (Wheeler & Rovet, 2007; Wheeler, Willoughby, McAndrews, & Rovet, 2011). However, we do not yet know whether their hippocampi function atypically when supporting specific memory abilities.

To determine if early life TH insufficiency due to CH affects hippocampal functioning, fMRI and a task specifically known to engage the hippocampus was used. In adults, fMRI studies have shown the hippocampus is preferentially involved when remembering associations between items versus the individual items (Giovanello, Schnyer, & Verfaellie, 2004; Kohler, Danckert, Gati, & Menon, 2005; Mayes et al., 2007) and parallel findings have been established regarding deficits for associative rather than item memory in adults with hippocampal damage (Holdstock, Mayes, Gong, Roberts, & Kapur, 2005; Mayes et al., 2004). Because of the paucity of fMRI studies examining children's medial temporal lobe functions, we modified a paradigm to use in the present study that was developed by Kohler et al. (2005) for adults. This task examining novelty effects (i.e., greater activation for new versus previously seen stimuli), demonstrated that hippocampal activation was particular to visuospatial associations (i.e., pairs of items and item-location relations). In contrast, extra-hippocampal areas of the medial temporal lobes were involved with item novelty effects (Kohler et al., 2005). Thus, to investigate the impact of early life TH insufficiency to memory functions supported by the hippocampus, we adapted the associative novelty paradigm of the study by Kohler et al. Given that both animal literature and the small relevant literature on brain structure and memory performance in CH suggest hippocampal dysfunction, we anticipated that the CH group would show an altered pattern of activation, although we could not predict exactly how this difference would be manifested in terms of greater or less activity in hippocampus.

METHOD

Participants

Participants ranged in age from 11.0 to 15.5 years. The majority were ascertained from existing databases of participants that included both CH and typically developing (TD) adolescents, while additional CH participants were recruited through the Division of Endocrinology at the Hospital for Sick Children (SickKids) and additional TD participants by posters placed within the hospital. Exclusionary criteria were exposure to alcohol or other teratogens during pregnancy, preterm birth, head injury, or a debilitating or chronic medical condition. Any participant wearing braces or having other metal implants was also excluded to ensure compatibility with MRI scanning requirements.

The CH group originally consisted of 17 adolescents (9 females). However, two were eliminated due to poor compliance/data corruption and one after being diagnosed with pseudoparahypothyroidism on the basis of her scans. Thus, the final CH sample consisted of 14 participants, one of whom was left handed. All children except two were identified by the Ontario newborn screening program, which uses a thyroid stimulating hormone (TSH) test; the two exceptions were a boy, whose sample failed to be delivered to the provincial laboratory by the courier and he was diagnosed clinically at 62 days of age, and a boy born abroad. The Canadian-born children were all diagnosed with CH by staff endocrinologists at SickKids, and the majority (9/14) were first treated within the first 2 weeks of life (mean age = 19.6 days). Three children with borderline TH levels were not treated until their T4 levels declined; two at 1 month of age and the third was unknown as he was diagnosed abroad[1]. On the basis of technetium scans conducted at the initial diagnostic visit, 8 children had ectopic glands, 2 had athyrosis, and 2 had dyshormonogenesis; etiologies were unknown for two children, one whose parents refused the scan and the other, who was born abroad and so not assessed in this way. Medical chart review revealed that at diagnosis, the CH group had a mean thyroid stimulating hormone (TSH) value of 139.67 mU/L and mean free thyroxine (T4) and total T4 values of were 8.53 pmol/L and 44.23 nmol/L, which fall well outside of the normal range for newborns (Rose & Brown, 2006). Their mean starting dose of L-T4 was 10.23 μg/kg/day.

The TD sample included children with a normal newborn screen and no evidence of later thyroid or other medical disorders. Any child with a history of learning disabilities or known neurological or psychiatric disorders was excluded. Of the 17 TD participants who originally met criteria, 1 was eliminated due to a periventricular cyst found on scanning and considered significant by the neuroradiologist and 1 due to a lack of responses during the fMRI session. Thus, the total TD control sample consisted of 15 adolescents, 2 of whom were left-handed. All procedures were approved by the research ethics board at SickKids and the University of Toronto.

Procedures

All participants underwent two days of testing as part of a larger study. On the first day, they received a battery of clinical tests that included tests of general intelligence and clinical tests of memory abilities (not reported here). On the second day, two fMRI studies were conducted in separate 1-hr sessions, the first involved the visuospatial memory paradigm described presently and the second, a verbal paired associates task, which is the topic of a separate study.

Participants received a gift certificate to use for lunch and/or a snack break and on completion of the scanning, received a CD with a structural picture of their own brain, a certificate of participation in the study, and a letter to use for mandatory high school volunteer hours. Parents were compensated for

[1] Given that this child was not diagnosed in Canada, we have less information about the duration and severity of his hypothyroidism early in life. However, when fMRI results were analyzed with and without this child, they were not altered. Therefore all results are reported with him included.

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parking and/or travel expenses. Neuroradiological reports were sent to the children's physicians with recommendations for follow-up if necessary.

Visuospatial Paired-Associates Task

This task based on a paradigm by Kohler et al. (2005) was redesigned to be child friendly and age appropriate by (a) using animal icons to remind the participants of the task demands, (b) presenting the different trial types as "games" to play, and (c) involving age-appropriate stimuli.

The experimental design is illustrated in Figure 1. Stimuli consisting of simple line drawings of objects were selected from a Snodgrass and Vanderwart-like set (Rossion & Pourtois, 2004). All stimuli were programmed for presentation using E-Prime software. For each participant, object stimuli were randomly paired and assigned to one of 12 unique spatial configurations within an invisible 4×6 grid. Placements were constrained so that the objects had to be separated by at least one square either up/down or left/right within the grid. Each spatial configuration was used twice to allow the object to be re-paired with a novel partner without also altering its spatial location.

Before scanning, participants received extensive practice with each of the "games." First, sample cards were used to illustrate the concept of each game and then participants practiced with the computer generated games, which used materials that would not appear during scanning. Encoding of the stimuli took place before functional imaging. During the first encoding session outside of the scanner, participants were presented with 24 pairs of objects in their assigned spatial configurations and instructed to remember both the pairs and their locations. Each object pair was shown for 4 s, followed by an inter-trial interval of 3 s. The full set of stimuli

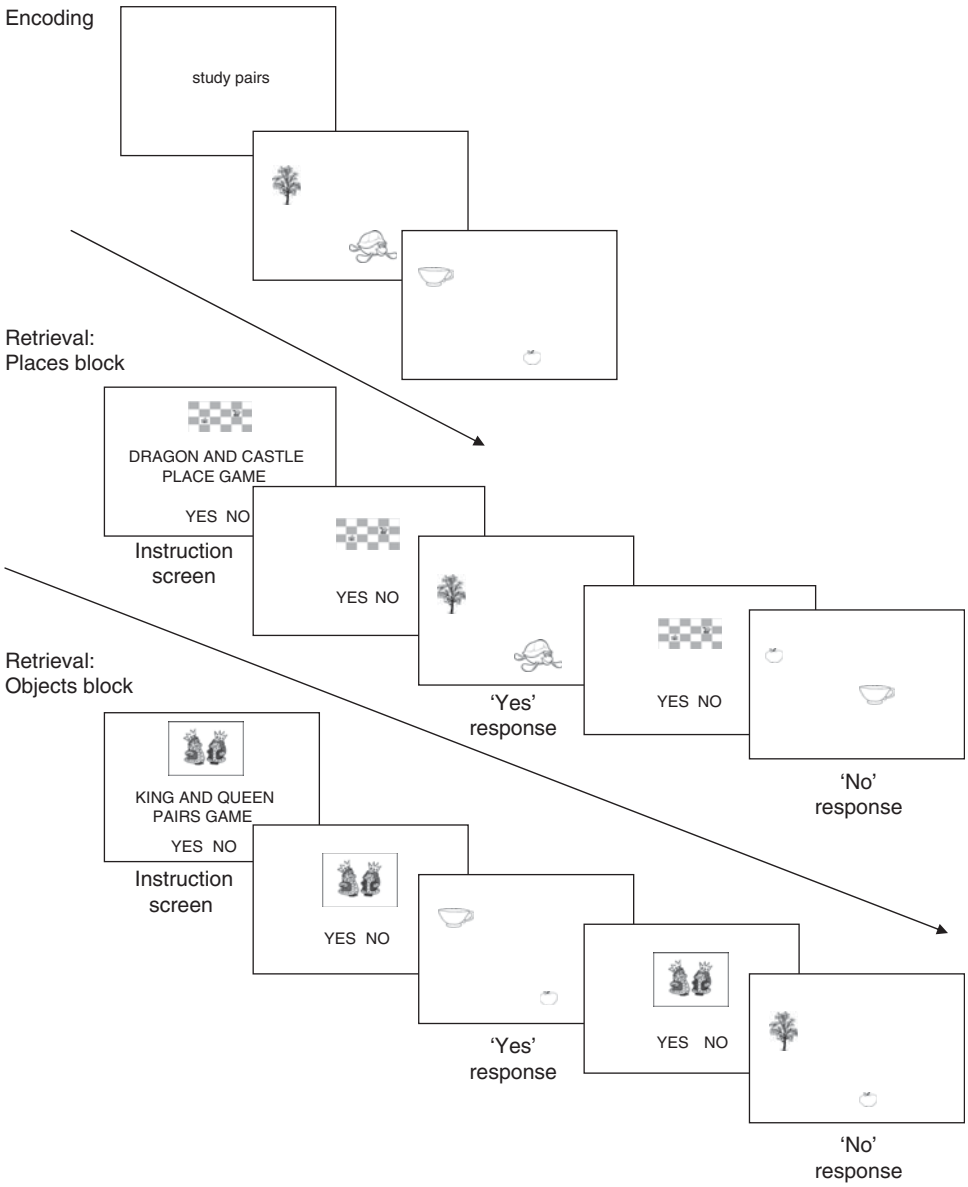


Fig. 1. Experimental design for encoding and retrieval of object pairs and locations.

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was shown twice to ensure adequate encoding of the material. Then in the scanner, participants first underwent a structural scan during which time the same stimuli were presented twice more to remind the participants of the list and ensure optimal learning and retention of information. Stimuli were presented via MR-compatible goggles.

The fMRI acquisition occurred during the recognition phase of the task, which was comprised of two retrieval conditions or "games." In the first game, participants had to decide if the displayed objects had been presented together during the study phase or if the pairing was new (Objects condition). The second game required participants to decide if object locations were the same as viewed previously or had been switched (Place condition). Retrieval task conditions were blocked, with each condition appearing once in each of three 10-min scans. The order of retrieval tasks during blocks and assignment of YES and NO response keys to the first or second button on the response pad were randomly assigned and counterbalanced across participants. Every retrieval block started with an "instruction" screen showing the game logo/cue and response button allocation for 10 s. This was then followed by 32 trials, 24 of which were previously seen associations requiring a "YES" response and 8 were novel associations requiring a "NO" response. Trials were presented in pseudorandom order and constrained such that novel trials could not be presented successively and no more than 6 old trials were consecutively presented. Retrieval trials lasted 9 s and consisted of the presentation of retrieval stimuli for 5 s followed by a 4-s fixation icon, which consisted of a small version of the game logo/cue to remind participants which retrieval task they were performing.

An important feature of this study design was the manipulation of only one variable at a time such that each retrieval trial involved alteration from the study phase on only one dimension. Either the pairing of the objects or the location of the objects within the pair was altered from the study phase, never both at once (see Figure 1). Another important aspect was that the retrieval tasks differed only as to the aspect of the association to which the participants attended and responded (Objects *vs.* Place), not the stimuli that were encoded. Thus, memory for object pairings and spatial locations were both assessed and compared using the same encoded material and no new objects were presented during the retrieval phrase.

Data Acquisition and Analysis

Functional data were acquired using echo-planar imaging (EPI) (repetition time = 2 s; 25 slices; 240 mm field of view; 64×64 matrix; resulting in a voxel size of $3.75 \times 3.75 \times 5$ mm) with an 8-channel head coil on the 1.5 Tesla Sigma GE SickKids' research scanner. Slices were acquired in a coronal-oblique orientation perpendicular to the long axis of the hippocampus. In each of the three runs, 304 functional volumes were acquired with the first 3 being dropped from the analyses to allow for signal equilibrium. E-prime software recorded behavioral data (accuracy and reaction time for each trial) for each participant. Correlations between all TH variables and behavioral data were assessed.

All functional imaging data were pre-processed and analyzed using SPM5 (Statistical Parametric Mapping 5; Wellcome Department of Imaging Neuroscience). Pre-processing included realigning and screening for excessive motion. Movement exceeding ± 1 mm and/or ± 1 degree rotation from baseline was noted for each run for each participant. Runs containing large motion spikes had the relevant scans removed and any run containing excessive motion throughout was discarded from the analyses. Further pre-processing included slice timing correction to the middle slice, normalizing using the Montreal Neurological Institute EPI template, resampling at a voxel size of $4 \times 4 \times 4$ mm, and smoothing using a Gaussian kernel of 8 mm full-width half maximum. Each stimulus event was modeled by SPM5's canonical hemodynamic response function beginning at the onset of each stimulus presentation. Only those trials in which the participant responded correctly were retained for analyses. First-level analyses of individual subjects' data were processed using a fixed-effects model to assess condition differences (i.e., New > Old) and those contrasts were then entered into second-level random-effects analyses to assess group differences. New > Old contrasts were of interest for both Objects and Place conditions given previous findings showing distinct novelty effects in the hippocampus for these different types of associative information (Kohler et al., 2005).

Since the primary focus of the present study was hippocampal activation, we applied a small volume correction using an ROI mask for the hippocampus from MAsks for Region of INterest Analysis software (MARINA; Walter et al., 2003) with a threshold of $p < .05$ and a minimum of five contiguous voxels. Covariates of no interest entered into the analyses were age and accuracy to remove the effects of individual variation in these parameters from the results. Percent signal change was extracted from a 3-mm sphere ROI around each peak activated voxel in each contrast between CH and TD groups using the MarsBaR-Marseille ROI toolbox (Brett, Anton, Valabregue, & Poline 2002). To determine the relationship between early TH levels (T4 and TSH at diagnosis) and hippocampal activation, multiple regressions were conducted in SPM5 for both Object and Place New > Old contrasts with the TH variable entered as the predictor of interest and age and accuracy were entered as covariates of no interest.

RESULTS

Demographic and Behavioral Data

Demographic data for both groups presented in Table 1 show CH and TD groups did not differ in age [$t(27) = 3.594$; $p = .07$], handedness [$\chi^2 = 0.299$; $p = .58$], or sex ratio [$\chi^2 = 0.042$; $p = .84$]. Behavioral data also shown in Table 1 reveal no group differences for either Object or Place in accuracy [$t(27) = 0.687$; $p = .50$; $t(27)1.303$; $p = .20$ respectively] or reaction time [$t(27) = 1.126$; $p = .27$; $t(27) = 0.618$; $p = .54$ respectively]. After accounting for

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Table 1. Demographic information and task performance

Variable	TD ($n = 15$)	CH ($n = 14$)
Age (years)	12.60 ± 1.32	13.41 ± 0.99
Male/female ratio	8/7	8/6
Handedness left/right	2/13	1/13
Accuracy (%)		
Object	81 ± 15	85 ± 13
Place	86 ± 13	77 ± 22
Reaction time (msec)		
Object	1739 ± 234	1644 ± 215
Place	1701 ± 273	1645 ± 203

TD = typically developing; CH = congenital hypothyroidism.

multiple comparisons, biomedical indices were not correlated with behavioral data in the CH group.

fMRI Results

Table 2 shows the peak activated voxels in the hippocampus for each of the planned contrasts and reveals novelty effects within both groups for both Object and Place New > Old contrasts. For the Objects condition, the TD group activated the left hippocampus, whereas the CH group activated bilateral hippocampi. Direct comparison of groups revealed the CH group showed areas of greater activation in both left and right hippocampi (see Figure 2 for SPM and percent signal change results from this contrast). In contrast, the TD group showed no areas of increased activity in the hippocampus relative to CH. In the Place condition, both TD and CH groups activated left and right hippocampi to a greater degree for novel than previously seen spatial configurations. A direct group comparison revealed greater activation in an area of the left hippocampus in CH relative to TD (see Figure 3 for SPM and percent signal change results from this contrast). Again, there were no areas of increased hippocampal activity in the TD relative to the CH group. Of note, although both groups showed novelty effects within the hippocampus for both Objects and Place conditions (see Table 2), percent signal change graphs from the voxel demonstrating maximal group differences (Figures 2 and 3) revealed the group differences were driven by the greater novelty effect in the CH group.

In the CH group, multiple regression analyses using biomedical data as predictors revealed that severity of hypothyroidism at time of diagnosis significantly predicted hippocampal activation for both Objects and Place novelty-related contrasts. TSH at diagnosis was positively correlated with bilateral hippocampal activations for both Object [$z = 2.42$; $p < .01$ right; $z = 3.40$; $p < .001$ left] and Place New > Old contrasts [$z = 2.28$; $p < .01$ right; $z = 2.60$; $p < .01$ left] while free T4 was negatively correlated with New > Old activations in the left hippocampus for the Object condition [$z = 2.00$; $p < .05$]. These associations signify that the more severe the child's hypothyroidism at time of diagnosis in early infancy (as indicated by a high TSH and a low free T4 level), the greater the hippocampal engagement over a decade later on a task designed to specifically evoke hippocampal engagement.

DISCUSSION

Using an associative novelty task to probe the functional integrity of the hippocampus, we found that adolescents with CH showed significantly increased activation relative to their TD peers. Specifically, we observed that the CH group showed greater activation in both left and right hippocampi for the Objects condition and increased activation in the left hippocampus for the Place condition. These findings,

Table 2. Hippocampal activation as a function of group and contrasts (small volume correction $p < .05$) with age and accuracy as covariates of no interest

		Peak coordinates (MNI)			
Analyses	Left or right hippocampus	x	y	z	*z*-value
Object (new > old object pairs)					
TD	L	−16	−32	−4	2.58
CH	L	−20	−32	−4	4.18
	R	28	−40	0	3.53
TD > CH	ns				
CH > TD	L	−28	−28	−8	2.48
	R	28	−40	0	3.37
Place (new > old spatial arrangement)					
TD	L	−20	−36	0	2.34
	R	24	−28	−8	2.95
CH	L	−24	−20	−16	2.31
	R	28	−24	−12	2.41
TD > CH	ns				
CH > TD	L	−24	−20	−16	2.56

TD = typically developing; CH = congenital hypothyroidism.

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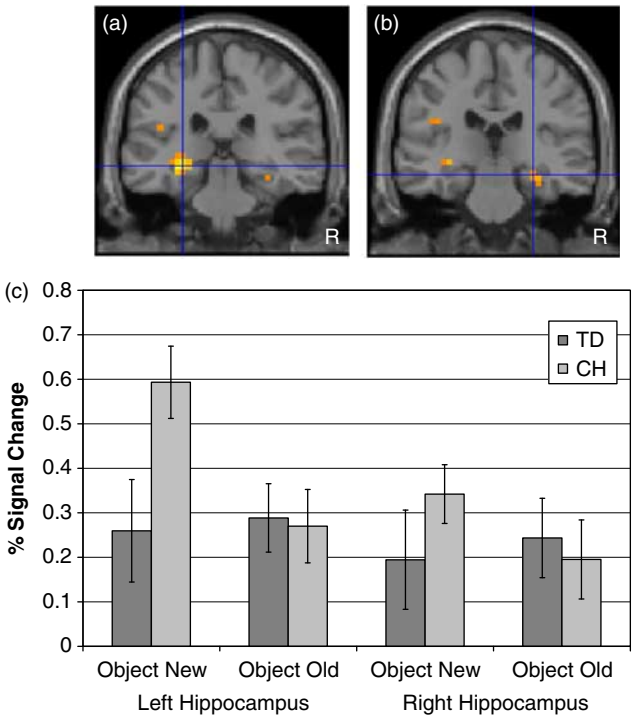


Fig. 2. SPM results for the congenital hypothyroid (CH) > typically developing (TD) contrast. a and b: Interaction between group and Object New > Old for left and right hippocampus; c: Percent signal change for each group at the peak activated voxel of the group × condition interaction.

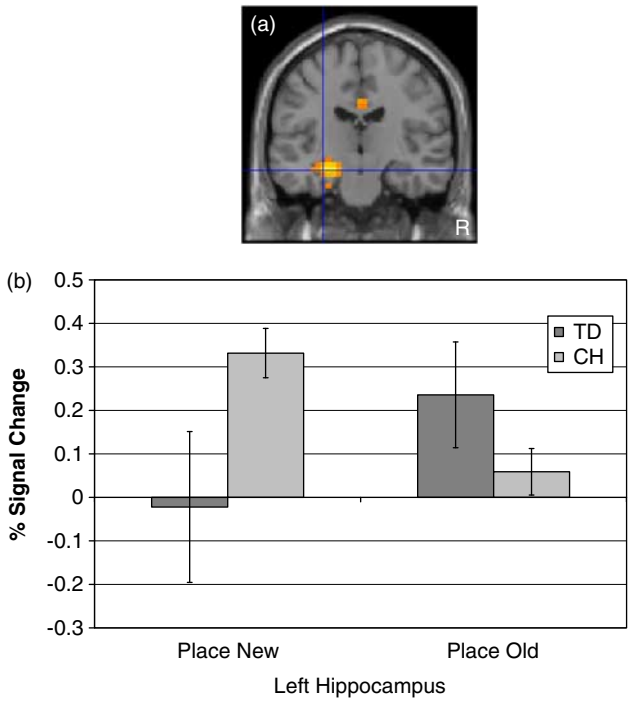


Fig. 3. SPM results for the congenital hypothyroid (CH) > typically developing (TD) contrast. a: Interaction between group and Place New > Old for left hippocampus; b: Percent signal change for each group at the peak activated voxel of the group × condition interaction.

therefore, indicate that adolescents with CH recruited additional neural resources to perform the task successfully and accomplish this by activating the left hippocampus to a greater degree than their TD peers across conditions and by also increasing the activation within their right hippocampus when their TD peers do not. Of note, increased hippocampal engagement in the CH group was present despite no significant differences in task performance relative to their TD peers and after statistically controlling for accuracy and age in the analyses to eliminate within-group variance due to these parameters.

In addition, the severity of TH deficiency at diagnosis predicted the degree of increased activation within the hippocampus in the CH group. Specifically, higher levels of TSH (which occur in response to insufficient TH) were associated with greater bilateral hippocampal activation in both Object and Place conditions. Similarly, lower T4 levels at diagnosis (signifying more severe hypothyroidism) were related to the extent to which the left hippocampus was active during the Object condition. Overall, these results indicate that TH levels early in life when the hippocampus is still undergoing development are critical for hippocampal functioning during adolescence and, if atypical, can lead to permanent alteration of functional integrity of this region.

Our finding of increased recruitment of hippocampal resources in the CH group when successfully performing a task is consistent with findings described for other adult patient populations with hippocampal damage. For example, patients with mild cognitive impairment exhibit increased recruitment of bilateral hippocampal resources to perform a memory task at the same level as controls (Dickerson et al., 2005). Similarly, the patient Jon, who acquired bilateral hippocampal damage in early life, showed bilateral recruitment of the hippocampus when controls only activated the left (Maguire, Vargha-Khadem, & Mishkin, 2001). To date, the few studies of hippocampal functioning in children or adolescents who sustained hippocampal damage have provided inconsistent findings. In some studies, increased activation relative to controls was seen (Gimenez et al., 2005; Maheu, 2008) while in others, no differences (Curtis, Zhuang, Townsend, Hu, & Nelson, 2006) or decreased or no hippocampal activation were reported (Chiu, 2009; Sowell et al., 2007). Thus, while the developmental literature suggests that early hippocampal insult has an impact on subsequent functioning, the nature and cause of these changes remain unclear. Given the relatively few studies conducted to date and a lack of consistent control over extraneous variables across studies, it is not evident whether the nature of the task or stimuli, cause or severity of the hippocampal damage, age at test or insult, or performance accuracy and overall memory abilities of the studied population were the critical factor(s) in influencing the results in these studies.

In addition, different biological processes may be contributing to the different findings across the patient populations studied to date. In terms of the CH population, extensive research on rodent models of TH insufficiency has provided insight as to potential mechanisms underlying altered activity in the hippocampus (e.g., Gilbert, 2004; Gilbert & Sui, 2006;

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Martínez-Galán et al., 1997; Rami, Patel et al., 1986; Rami, Rabie et al., 1986), particularly in the context of memory operations engaged by the task in the present study. According to one current model, associative novelty detection in the hippocampus has been proposed to operate via a comparator mechanism that identifies a mismatch between expectations based on prior experiences and current sensory information (Kumaran, 2007). Two critical areas for associative novelty detection (i.e., DG and CA1) are known to be affected by the lack of TH in rodent models of CH. Lack of TH during early development results in reduced numbers of cells within the DG (Rami, Rabie et al., 1986) and area CA1 (Martínez-Galán et al., 1997) as a result of impaired migration of cells to these regions (Martínez-Galán et al., 1997; Rami, Rabie et al., 1986). There are also morphological alterations within the granule cells of the DG and the pyramidal cells of Ammon's horn resulting in reduced arborization of dendritic fields (Rami, Rabie et al., 1986). Thus, the animal literature has shown that the structure of the hippocampus is altered by a lack of TH during development in regions that appear to subserve associative novelty processes.

The structural alterations described also have functional consequences. In both the DG and area CA1 under baseline conditions and following induction of long-term potentiation, the hippocampal neurons are less responsive to input and not as likely to fire from the same level of input as a control animal. In addition, once the input is sufficient to cause the cell to fire, the output is larger (Gilbert, 2004; Gilbert & Sui, 2006). Thus, these processes may contribute to the increased hippocampal activation observed presently in the CH group and may provide a biological basis for the weaker memory abilities associated with CH.

The findings from the present study also have implications for understanding memory functioning in CH. Given the CH group showed recruitment of increased resources relative to controls during a relatively easy (by accuracy criteria) associative recognition memory task, it is possible that tasks which challenge hippocampal engagement, or coordination of hippocampal and neocortical networks, to a greater extent may exceed those resources. This may be reflected in the relative weaknesses and subtle decrease in clinical memory scores previously observed in studies of CH (Oerbeck et al., 2005; Rovet, 1999). However, as the present study did not examine fMRI activation in adolescents with CH using more challenging memory tasks, it remains purely speculative as to how the CH hippocampus would function under such circumstances. In addition, the relevance of the type of stimuli used presently is not known and whether results would be similar had other types of memory stimuli been used. A forthcoming study using a verbal paired associates memory task will address this issue. In addition, since the present study was not designed to investigate activity within the entire episodic memory network, it is not known to what degree differences in other brain regions which may also be affected by early TH insufficiency are contributing to present findings. Furthermore, this study did not investigate if the differences in hippocampal activity are stable or change further with development. Finally, TH levels at time of assessment and scanning, which could have affected cognitive functioning (Rovet, 2002; Song et al., 2001), were not determined.

In conclusion, even though adolescents with CH and TD adolescents performed comparably during a visuospatial associative memory task, they differed in their hippocampal activation patterns such that the CH group showed increased hippocampal activation relative to TD. The present study, therefore, supports the view that an early TH deficiency at a time when the hippocampus is undergoing critical development has long-lasting effects on subsequent functioning and necessitates the recruitment of additional hippocampal resources. These results indicate that even well-treated CH can impact hippocampal functioning and also demonstrate how a brain structure/network that is compromised early in development compensates to maintain performance.

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