Effects of Early Thyroid Hormone Deficiency on Autobiographical Memory and Hippocampal Structure and Function during Late Childhood and Early Adolescence

by

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Abstract

The hippocampus, which is a critical brain region for episodic autobiographical memory (AM), is particularly vulnerable to damage following periods of early thyroid hormone (TH) deficiency. Although numerous studies have examined AM performance in adult patients with hippocampal damage, no study has yet examined AM in children exposed to early TH deficiency, such as children with congenital hypothyroidism (CH) and offspring of women who were hypothyroid during pregnancy (HYPO). Given that both animal and human studies have shown that early TH deficiency results in significant hippocampal abnormalities and memory impairments, the purpose of this dissertation was to investigate the effects of early TH deficiency on AM and hippocampal structure and function during childhood.

Study I examined AM performance in a large sample of typically developing children and adolescents in order to validate the use of the newly-developed Children’s Autobiographical Interview (CAI). In Study II, the CAI was used to investigate AM performance in children with early TH deficiency (i.e., CH and HYPO groups). Similar to the findings observed in adults with hippocampal damage, CH and HYPO groups both exhibited weaknesses in episodic AM, but not semantic AM, relative to controls. In addition, structural MRI revealed mild bilateral
hippocampal volume reductions in HYPO, but not CH, which is consistent with animal models suggesting that early prenatal TH deficiency (i.e., HYPO) may be associated with greater abnormalities in hippocampal structure than postnatal TH deficiency (i.e., CH). Study III investigated children’s AM accuracy performance using a staged event and indicated that children with early TH deficiency had proportionally less accurate recollections of the staged event than controls. Importantly, smaller hippocampal volumes in both CH and HYPO groups predicted lower AM accuracy scores. Finally, in Study IV, functional MRI revealed that children with early TH deficiency exhibited abnormal (i.e., greater bilateral) hippocampal activation during episodic AM retrieval, but not during semantic AM retrieval, relative to controls, which may reflect neural compensation or may be a by-product of the degree of hippocampal damage. Overall, this dissertation provides critical new insight into the long-term effects of early TH deficiency on children’s AM performance and the hippocampus.
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Table of Contents

Abstract ........................................................................................................................................ II

Acknowledgements ..................................................................................................................... IV

Table of Contents ....................................................................................................................... VI

List of Tables ................................................................................................................................ XI

List of Figures ............................................................................................................................... XIII

List of Appendices ...................................................................................................................... XVI

Chapter 1
General Introduction

1.1 Overview of Early Thyroid Hormone Deficiency ................................................................ 2

  1.1.1 Hippocampal Development and the Impact of Early Thyroid Hormone Deficiency .... 3

  1.1.2 Maternal Hypothyroidism During Pregnancy and Associated Child Outcomes ...... 8

  1.1.3 Congenital Hypothyroidism and Associated Child Outcomes ................................ 10

  1.1.4 Summary and Model of Early Thyroid Hormone Deficiency .................................... 12

1.2 Overview of Autobiographical Memory (AM) ................................................................ 13

  1.2.1 Episodic and Semantic AM in Typically Developing Children .................................. 14

  1.2.2 Episodic and Semantic AM in Patients With Hippocampal Damage ....................... 17

  1.2.3 Functional Neuroanatomy of AM Retrieval and the Essential Role of the Hippocampus
       ............................................................................................................................................... 20

1.3 Objectives of the Present Research .................................................................................... 22

Chapter 2
Study I: Episodic and Semantic Autobiographical Memory in Typically Developing Children and Adolescents

2.1 Introduction ......................................................................................................................... 30

2.2 Methods ............................................................................................................................... 33
2.2.1 Participants

2.2.2 General Procedure

2.2.3 Demographic Information

2.2.4 Children’s Autobiographical Interview

2.2.4.1 Scoring Protocol for the Children’s Autobiographical Interview

2.2.5 Everyday Memory Questionnaire

2.2.6 Data Analysis

2.3 Results

2.3.1 Effect of Age on AM Performance in the Recall Condition

2.3.2 Effect of Age on AM Performance in the Recall + Specific Probe Condition

2.3.3 Effect of Participants’ Visualization Ratings on Episodic AM Performance

2.3.4 Effect of Age on Everyday Memory and its Relation to Episodic AM

2.4 Discussion

Chapter 3

Study II: Effects of Early Thyroid Hormone Deficiency on Children’s Episodic and Semantic Autobiographical Memory Performance and Hippocampal Volumes

3.1 Introduction

3.2 Methods

3.2.1 Participants

3.2.2 General Procedure

3.2.3 Demographic Information

3.2.4 Early TSH Levels and TH Treatment Values for CH and HYPO

3.2.5 Clinical Neuropsychological Assessment of Intelligence and Memory

3.2.6 Everyday Memory Questionnaire
Chapter 3

3.2.7 Children’s Autobiographical Interview .................................................. 61
3.2.7.1 Scoring Protocol for the Children’s Autobiographical Interview .............. 61
3.2.8 Structural MRI Acquisition, Processing, and Hippocampal Volumes .......... 62
3.2.9 Data Analysis ......................................................................................... 63

3.3 Results ....................................................................................................... 66
3.3.1 Early TSH Levels and TH Treatment Values for CH and HYPO .................. 66
3.3.2 Demographic and Clinical Neuropsychological Test Results ...................... 67
3.3.3 Group Differences in AM Performance in the Recall Condition ................. 67
3.3.4 Group Differences in AM Performance in the Recall + Specific Probe Condition 69
3.3.5 Group Differences in Visualization Ratings and its Effect on Episodic AM .... 70
3.3.6 Group Differences in Hippocampal Volumes and its Effect on Episodic AM .... 70
3.3.7 Effects of TH Deficiency Severity on Hippocampal Volumes, Clinical Memory Scores, and Episodic AM ......................................................................................................... 71

3.4 Discussion ................................................................................................. 72

Chapter 4

Study III: Accuracy of Episodic Autobiographical Memory in Children with Early Thyroid Hormone Deficiency Using a Staged Event

4.1 Introduction ............................................................................................... 88
4.2 Methods ..................................................................................................... 91
4.2.1 Participants ............................................................................................. 91
4.2.2 General Procedure .................................................................................. 93
4.2.3 Demographic Information and Assessment of Intelligence ....................... 94
4.2.4 Early TSH Levels and TH Treatment Values for CH and HYPO ............... 94
4.2.5 Children’s Autobiographical Interview .................................................. 95
4.2.5.1 Scoring Protocol for the Children’s Autobiographical Interview .......... 95
4.2.6 Structural MRI Acquisition, Processing and Hippocampal Volumes ___________96
4.2.7 Data Analysis_________________________97
4.3 Results_____________________________________________________________99
  4.3.1 Demographic Measures________________________________________________99
  4.3.2 Group Differences in AM performance in the Recall + Specific Probe condition ____99
  4.3.3 Group Differences in Visualization Ratings and its Effects on Episodic AM____101
  4.3.4 Group Differences in Hippocampal Volumes and its Effects on Episodic AM ____101
  4.3.5 Effects of TH Deficiency Severity on Proportion Accuracy Scores __________102
4.4 Discussion__________________________________________________________102

Chapter 5
Study IV: Hippocampal Activation during Episodic and Semantic Autobiographical Memory Retrieval in Typically Developing Children and Children with Early Thyroid Hormone Deficiency

5.1 Introduction________________________________________________________114
5.2 Methods_________________________118
  5.2.1 Participants ____________________________118
  5.2.2 General Procedure_________________________119
  5.2.3 Demographic Information and Assessment of Intelligence ______________120
  5.2.4 Early TSH Levels and TH Treatment Values for CH and HYPO__________120
  5.2.5 Pre-scan Interview_________________________________________________120
  5.2.6 Structural MRI Acquisition, Processing, and Hippocampal Volumes________121
  5.2.7 Functional MRI Task________________________________________________121
  5.2.8 Pretraining and Functional MRI Scanning______________________________122
  5.2.9 Functional MRI Data Acquisition and Processing________________________123
  5.2.10 Functional MRI Data Analysis________________________________________125
5.2.11 Behavioural, Hippocampal Volume, and Early TSH Data Analysis ___________126

5.3 Results_______________________________________________________________127

5.3.1 Demographic and Hippocampal Volume Results ____________________________127

5.3.2 Behavioural Results___________________________________________________127

5.3.3 fMRI Results: Group Differences in Hippocampal Activation________________128

5.3.3.1 Episodic AM Retrieval: PE > GS Contrast_______________________________128

5.3.3.2 Episodic AM retrieval: PE > PS Contrast _______________________________128

5.3.3.3 Semantic AM Retrieval: PS > GS Contrast_______________________________129

5.3.3.4 Semantic AM Retrieval: PS > PE Contrast_______________________________129

5.3.4 fMRI Results: Predictors of Hippocampal Activation ________________________129

5.3.4.1 Effect of Total Hippocampal Volumes on Hippocampal Activation__________129

5.3.4.2 Effect of PE Accuracy Scores on Hippocampal Activation_________________130

5.3.4.3 Effect of Participants’ Visualization Ratings on Hippocampal Activation____130

5.3.4.4 Effect of TH Deficiency Severity on Hippocampal Activation_______________130

5.4 Discussion____________________________________________________________131

Chapter 6
General Discussion

6.1 Summary of the Results _________________________________________________152

6.2 General Limitations_____________________________________________________157

6.3 Implications of Findings_______________________________________________159

6.4 Future Directions______________________________________________________162

6.5 General Conclusion____________________________________________________165

References_____________________________________________________________166

Appendices ______________________________________________________________183
List of Tables

Table 2.1. Number of Males and Females at Each Age Group__________________________46

Table 2.2. Regressions with Age Predicting Episodic and Non-episodic Details in the Recall Condition after Controlling for Retention Interval and Sex____________________________47

Table 2.3. Regressions with Age Predicting Episodic and Non-episodic Details in the Recall + Specific Probe Condition after Controlling for Retention Interval and Sex________________49

Table 2.4. Means and Standard Deviations (in Parentheses) of the EMQ Composite and Two Subscales Across Age__________________________________________________________51

Table 3.1. Group Means and Standard Deviations (in Parentheses) for Early Thyroid Stimulating Hormone (TSH) Values and Thyroid Hormone (TH) Treatment Values for CH and Mothers of HYPO________________________________________________________78

Table 3.2. Frequency Scores, Group Means, and Standard Deviations (in Parentheses) for Demographic and Clinical Neuropsychological Measures_______________________________________________79

Table 3.3. Group Means and Standard Deviations (in Parentheses) for Intracranial Volumes and Hippocampal Volumes __________________________________________________________80

Table 4.1. Group Means and Standard Deviations (in Parentheses) for Early Thyroid Stimulating Hormone (TSH) Values and Thyroid Hormone (TH) Treatment Values for CH and Mothers of HYPO________________________________________________________107

Table 4.2. Descriptions and Examples of Inaccurate and Accurate Episodic Details of the Staged Event______________________________________________________________108

Table 4.3. Frequency Scores, Group Means, and Standard Deviations (in Parentheses) for Demographic Measures and Hippocampal Volumes_________________________________________109
Table 5.1. Group Means and Standard Deviations (in Parentheses) for Early Thyroid Stimulating Hormone (TSH) Values and Thyroid Hormone (TH) Treatment Values for CH and Mothers of HYPO

Table 5.2. Frequency Scores, Group Means, and Standard Deviations (in Parentheses) for Demographic Measures, Intracranial Volumes, and Hippocampal Volumes

Table 5.3. Group Means and Standard Deviations (in Parentheses) for fMRI Behavioural Data

Table 5.4. Significant Peak Activations in the Hippocampus Across Groups for Each Contrast (p < .05, FDR, SVC), After Controlling for Total Hippocampal Volumes and PE Accuracy Scores

Table 5.5. Results of the Regression Analyses (p < .10, SVC) for the PE > GS Contrast
List of Figures

Figure 1.1. Depiction of how Thyroid Hormone (TH) Influences Fetal Brain Neurodevelopment
_________________________________________________________________________________________23

Figure 1.2. Estimated Timeline Illustrating the Source of Thyroid Hormones (TH) During
Gestation (a) and Key Neurodevelopmental Events Within the Cortex and Hippocampus (b) from
Conception to 6 Months of Life_________________________________________________________________24

Figure 1.3. Diagrams of the Two Subregions of the Hippocampus, the Cornu Ammonis (CA)
Fields (Light Gray) and Dentate Gyrus (DG; Black), from a Transverse View (a) and Coronal
View (b) ______________________________________________________________________________25

Figure 1.4. Estimated Timeline of Rat Neurodevelopment Within the Hippocampus from
Conception, Gestational Day (GD) 0, to the End of the First Year of Life, Postnatal Day (PND)
20 _____________________________________________________________________________________26

Figure 1.5. Neural Circuitry Within the Hippocampus, Including the Perforant Path and the
Direct Pathway __________________________________________________________________________27

Figure 1.6. Illustration of the Hypothalamus-Pituitary-Thyroid Axis and Negative Feedback
System for Thyroid Hormone (TH) Production ____________________________________________________________________________________________28

Figure 1.7. Significant Regions of Peak Activation During AM Retrieval Reported in Svoboda et

Figure 2.1. Mean Number of Total Episodic and Total Non-Episodic Details Recalled at Each
Age Across the Two Conditions: Recall (a) and Recall + Specific Probe (b)_______________________52

Figure 3.1. Manual Tracings of Anterior (White) and Posterior (Dark Gray) Subregions of the
Left and Right Hippocampus Using ANALYZE 9.0 Software _______________________________________________________________________________81

Figure 3.2. Individual TSH Levels from One Month of Age to the Current Age of Testing in
Children with Congenital Hypothyroidism (N = 25) ________________________________________________________________________________________82

XIII
Figure 3.3. Group Means for the Number of Total Episodic and Total Non-Episodic Details Recalled Across the Two Conditions: Recall (a) and Recall + Specific Probe (b)__________83

Figure 3.4. Group Means for the Number of Details Recalled in Each Episodic Detail Subcategory Across the Two Conditions: Recall (a) and Recall + Specific Probe (b)__________84

Figure 3.5. Group Means for the Number of Details Recalled from Each Non-Episodic Detail Subcategory Across the Two Conditions: (a) Recall and (b) Recall + Specific Probe__________85

Figure 3.6. Group Means for the Number of Visual and Non-Visual Details Recalled in the Recall + Specific Probe Condition ______________________________________________________11

Figure 3.7. Scatterplots of Maternal TSH Values During the Third Trimester by Right Anterior Hippocampal Volumes (a) and Delayed Visuospatial Memory Scores (b) in the HYPO Group_87

Figure 4.1. Group Means for Proportion Accuracy Scores (a) and the Number of Total Inaccurate and Total Accurate Details Recalled (b) in the Recall + Specific Probe Condition_110

Figure 4.2. Group Means for the Number of Details Recalled from Each Inaccurate Episodic Detail Subcategory (a) and Each Accurate Episodic Detail Subcategory (b) in the Recall + Specific Probe Condition ______________________________________________________111

Figure 4.3. Scatterplots of Total Hippocampal Volumes by Proportion Accuracy Scores from the Staged Event for Controls (a), HYPO (b), and CH (c)_____________________________112

Figure 4.4. Scatterplots of Early Thyroid Stimulating Hormone (TSH) Values by Proportion Accuracy Scores from the Staged Event for HYPO (a) and CH (b)_________________________113

Figure 5.1. Direct Comparison of Episodic AM Retrieval and General Semantic Retrieval (PE > GS) in the TH-Deficient Group (a), Controls (b), and the TH-Deficient Group > Controls Comparison (c)_________________________________144
Figure 5.2. Direct Comparison of Episodic AM Retrieval and Semantic AM Retrieval (PE > PS) in TH- TH-Deficient Group (a), Controls (b), and the TH-Deficient Group > Controls Comparison (c)_________________________________ 145

Figure 5.3. Direct Comparison of Semantic AM Retrieval and General Semantic Retrieval (PS > GS) in the TH-Deficient Group (a) and Controls (b)________________________146

Figure 5.4. Significant Medial Temporal Lobe Activity During Episodic AM Retrieval (i.e., the PE > GS Contrast) that was Negatively Correlated with Total Hippocampal Volumes in the TH-Deficient Group (a) and Positively Correlated with Total Hippocampal Volumes in Controls (b) ______________________________________________________________147

Figure 5.5. Significant Medial Temporal Lobe Activity During Episodic AM Retrieval (i.e., the PE > GS Contrast) that was Positively Correlated with PE Accuracy Scores in the TH-Deficient Group (a) and Controls (b)_____________________________________________________________148

Figure 5.6. Significant Medial Temporal Lobe Activity During Episodic AM Retrieval (i.e., the PE > GS Contrast) that was Positively Correlated With Participants’ Visualization Ratings in the TH-Deficient Group ___________________________________________________________149

Figure 5.7. Significant Medial Temporal Lobe Activity During Episodic AM Retrieval (i.e., the PE > GS Contrast) that was Positively Correlated With TH Deficiency Severity (i.e., Elevated TSH Levels) in HYPO (a) and CH (b)_________________________________________________________150
List of Appendices

Appendix A. Comparison Between the Children’s Autobiographical Interview and Levine et al.’s (2002) Autobiographical Interview for Adults________________________________________________________190

Appendix B. Instructions for the Children’s Autobiographical Interview from Study I________191

Appendix C. Sample Autobiographical Events Provided to Participants to Facilitate AM Retrieval________________________________________________________192

Appendix D. Scoring Example Using the Autobiographical Interview Scoring Manual________193

Appendix E. Descriptions and Examples of Experimenter Ratings using the Autobiographical Interview Scoring Manual________________________________________194

Appendix F. Skewness and Kurtosis Values for Variables that were Significantly Deviated in Study I________________________________________________________196

Appendix G. Skewness and Kurtosis Values for Variables that were Significantly Deviated in Study II________________________________________________________197

Appendix H. Non-Parametric Mann-Whitney Tests for Group Differences in AM Performance in Study II__________________________________________________________________________________________198

Appendix I. Boxplots across groups for hippocampal volume, delayed visuospatial memory, and severity of maternal TH deficiency variables________________________________________________________199

Appendix J. Instructions for the Staged Autobiographical Event in Study III __________200

Appendix K. Staged Event Instructions and Examiner Script for Study III______________201

Appendix L. Probing Questions from the Specific Probe Phase of the CAI for Study III____204

Appendix M. Non-Parametric Mann-Whitney Tests for Group Differences in AM Performance in Study III__________________________________________________________________________________________206

Appendix N. Personal Semantic Questionnaire for Study IV________________________207

Appendix O. Functional MRI Sentence Verification Task for Study IV________________209
Appendix P. General Semantic Questions Adapted from Rekkas and Constable (2005) and Used in the fMRI Sentence Verification Task for Study IV

Appendix Q. Instructions for the fMRI Task for Study IV
Chapter 1
General Introduction

The studies presented in this dissertation were conducted to investigate whether early thyroid hormone (TH) deficiency may have adverse effects on episodic autobiographical memory (AM), as well as hippocampal structure and function, during childhood. The hippocampus was targeted for investigation because it plays a critical role in episodic AM and is particularly susceptible to damage following early periods of TH deficiency (Madeira et al., 1992; Moscovitch, 2008). In particular, I examined whether children with early TH deficiency exhibited reduced hippocampal volumes using structural magnetic resonance imaging (MRI), which provides a 3D anatomical image of the brain. In addition, I examined whether reductions in hippocampal volume might contribute to weaknesses in episodic AM recall and accuracy performance in children with early TH deficiency. In order to investigate hippocampal function, I used functional MRI, which provides an indirect measure of the location of task-related neural activity by measuring the blood oxygenation level-dependent (BOLD) response. More specifically, I examined whether children with early TH deficiency exhibited abnormal hippocampal activation during episodic AM retrieval relative to typically developing controls.

The purpose of this introduction is three-fold. First, I provide an overview of the effects of early TH deficiency on hippocampal development and introduce two conditions of early TH deficiency, namely maternal and congenital hypothyroidism. Both conditions have been associated with memory and visuospatial impairments, but because they differ in their specific timing of TH loss during gestation, they may be associated with different abnormalities in hippocampal structure and function (Ausó et al., 2004; Hasegawa et al., 2010; Man et al., 1991; Mirabella et al., 2005). Within the overview of early TH deficiency, I also outline a model of prenatal versus postnatal TH deficiency by contrasting the effects of maternal and congenital hypothyroidism on hippocampal structure and function. Second, I provide an overview of
episodic and semantic AM performance in both typically developing children and patients with hippocampal damage, in order to set the context for investigating AM in children with early TH deficiency and abnormal hippocampal development. Within this overview, I also discuss the functional neuroanatomy of AM retrieval and highlight the essential role of the hippocampus in episodic AM retrieval. Finally, I provide an overview of the main objectives of the four studies presented in this dissertation.

1.1 Overview of Early Thyroid Hormone Deficiency

Thyroid hormone (TH) plays an essential role in early brain development because it is involved in regulating several fundamental neurobiological processes (Bernal & Nunez, 1995; Koibuchi & Chin, 2000). For example, TH exerts its actions directly in neurons where it activates the transcription of genes that control neurogenesis, neuronal migration, synaptogenesis, dendrite proliferation, and myelination (see Figure 1.1; Chan & Rovet, 2003; Williams 2008). When the developing brain is exposed to insufficient TH levels, transcription of these TH-dependent genes is repressed, resulting in significant alterations in the structure and function of certain brain regions (Bernal, 2007). One brain region that is particularly vulnerable to early TH deficiency is the hippocampus (Gilbert & Paczkowski, 2003; Madeira et al., 1992), which is essential for episodic autobiographical memory (AM; i.e., remembering specific past events) and for retrieving visuospatial information (Hoscheidt, Nadel, Payne, & Ryan, 2010; Moscovitch, 2008). For example, animal models of TH deficiency during gestation have shown that TH-deficient rats exhibit irreversible changes in hippocampal structure as well as functional impairments in learning and memory (Ausó et al., 2004; Gilbert & Sui, 2006; Lavado-Autric et al., 2003).

In humans, the effects of early TH deficiency can be best examined by contrasting two clinical populations that differ in the timing and source of TH loss during gestation and in the first few months of life. These two populations are offspring of women who were hypothyroid
during pregnancy (HYPO) and individuals with congenital hypothyroidism (CH; Zoeller & Rovet, 2004). During the first half of gestation, the fetus is entirely dependent on the maternal TH supply since the fetal thyroid gland does not fully form until the second trimester and is not fully functional until birth (see Figure 1.2a; Calvo et al., 2002; Chan & Rovet, 2003). Although the fetus begins to produce its own TH in increasingly larger quantities in the second half of gestation, the maternal contribution of TH still continues to play an important role until its transfer is severed at birth (see Figure 1.2a; Morreale de Escobar, Obregón, & Escobar del Rey, 2004; Vulsma, Gons, & de Vijlder, 1989). Thus, in cases of maternal hypothyroidism during pregnancy, the fetus receives insufficient levels of maternal TH throughout gestation; however, greater severity of TH deficiency is typically observed in the first half of gestation because the fetal thyroid gland is not yet functional (Zoeller & Rovet, 2004). In contrast, a fetus with CH is unable to produce sufficient levels of its own TH during late gestation and after birth due to abnormal development of the fetal thyroid gland (Zoeller & Rovet, 2004). Therefore, an individual with CH undergoes a late prenatal and postnatal period of TH deficiency that continues until TH treatment is provided (Zoeller & Rovet, 2004). Despite the fact that animal models of HYPO and animal models of CH have both shown that early TH deficiency is associated with adverse effects on hippocampal development and memory function, no study has yet directly compared children with CH and children of hypothyroid women in terms of hippocampal structure and function, as well as memory performance. In addition, no study has yet examined whether these children show deficits in episodic AM, which is critically dependent on the hippocampus.

1.1.1 Hippocampal Development and the Impact of Early Thyroid Deficiency

The hippocampus is a medial temporal lobe structure that plays a crucial role in the formation, consolidation, and retrieval of episodic AMs (Eldridge, Knowlton, Furmanski, Bookheimer,
Engel, 2000; Moscovitch, 2008; Ryan et al., 2001). More specifically, the hippocampus binds patterns of neural activity present at the time of encoding into a memory trace that can be sustained and retrieved over time (Buckner & Wheeler, 2001; Eichenbaum, 2000; Eichenbaum & Bunsey, 1995). Importantly, the hippocampus is also one of several brain regions that require an adequate supply of TH throughout gestation and after birth for proper neurodevelopment (Bernal & Nunez, 1995).

Within the hippocampus, there are two distinct subregions, the dentate gyrus and the cornu ammonis (CA 1-4) fields that differ in size, function, and rate of development (see Figure 1.3; Madeira et al., 1992; Seress, Ábrahám, Tornóczky, & Kosztolányi, 2001). For example, the large CA fields develop early in gestation, with cell formation and neuronal migration in this subregion being largely complete by the end of the second trimester (see Figure 1.2b; Seress et al., 2001). In particular, the CA1 field, which comprises the largest portion of the hippocampus (i.e., 65% of the combined volume of the CA fields and dentate gyrus; Harding, Halliday, & Kril, 1998), is the first region of the hippocampus to develop during gestation (Arnold & Trojanowski, 1996). In contrast, the smaller dentate gyrus, which comprises only 5% of the hippocampus (Harding et al., 1998), does not fully develop until the first year of life and does not reach functional maturity until approximately two years of age (see Figure 1.2b; Bachevalier & Vargha-Khadem, 2005; Seress et al., 2001). In addition, the dentate gyrus appears to increase in size throughout childhood and adolescence and is one of the few brain regions to generate new neurons throughout adulthood (Eriksson et al., 1998; Gogtay et al., 2006; Mathews et al., 2010). Unlike the CA1 field, which is thought to play an important role in memory consolidation and retrieval, the dentate gyrus is thought to be uniquely involved in memory encoding and initiating temporal associations during the early stages of memory formation (Aimone, Wiles, & Gage, 2006; Daumas, Halley, Frances, & Lassalle, 2005; Jerman, Kesner, & Hunsaker, 2006; Vago, Bevan, & Kesner, 2007). Given the different developmental trajectories of the CA1 field and
dentate gyrus, the exact timing and severity of TH deficiency can have a significant impact on which hippocampal subregion is affected as well as the extent of the structural impairments.

Despite differences in the timing of neurodevelopment between humans and rats (see Figures 1.2b and 1.4 to compare human and rat neurodevelopmental timelines), animal models of early TH deficiency have provided an important avenue for investigating the effects of maternal and congenital hypothyroidism on hippocampal structure and function. For example, animal research has shown that maternal TH deficiency during early gestation significantly impairs neurogenesis, neuronal migration, and synaptic function in offspring, particularly in the early-developing CA1 field (Ausó et al., 2004; Madeira et al., 1992). When pregnant rats were rendered hypothyroid during gestational days 12-15 (i.e., equivalent to the second trimester in humans), they produced offspring that had reduced cell numbers and abnormal patterns of neuronal migration in the CA1 field (Ausó et al., 2004; Cuevas et al., 2005). In particular, the hippocampally-destined neurons became permanently trapped in aberrant locations, such as in the outermost layer of the hippocampus (i.e., the alveus) and in subcortical white matter (Ausó et al., 2004; Lavado-Autric et al., 2003). In addition, other studies have shown that maternal TH deficiency during gestational days 12-15 impairs long-term potentiation (i.e., a form of synaptic plasticity that is necessary for binding information and is a cellular correlate of learning and memory), as well as spatial learning and memory performance on water maze tasks in HYPO offspring (Liu et al., 2010; Opazo et al., 2008). Thus, it appears that reduced cell numbers and abnormal migration of neurons within the CA1 field may alter the establishment of normal circuits and lead to functional deficits in learning and memory. Importantly, researchers have shown that TH treatment after gestational day 15 in rats (i.e., treatment during late gestation or early postnatal life) does not reverse the structural abnormalities associated with early prenatal TH deficiency, suggesting that the first half of gestation is an important sensitive period for the
cytoarchitecture of the developing hippocampus (Ausó et al., 2004; Lavado-Autric et al., 2003; Madeira et al., 1992).

Only one animal study to date has examined the effects of TH deficiency specifically during the third trimester, when both HYPO and CH groups experience some degree of TH loss (see Figure 1.2a; Berbel et al., 2010). In this study, pregnant rats that were rendered hypothyroid from gestational day 16 to postnatal day 0 (i.e., equivalent to the first half of the third trimester in humans), produced offspring who exhibited abnormal cytoarchitecture in the parietal cortex and had a greater number of heterotopic (i.e., abnormally located) neurons within the outer layers of the anterior CA1 field of the hippocampus (Berbel et al., 2010). In addition, these offspring exhibited delayed learning on an aversive memory retrieval task because they were less likely to avoid a foot-shock after a delay period than control rats (Berbel et al., 2010). According to Berbel et al. (2010), their results indicate that maternal TH deficiency during late gestation also impairs neuronal migration and leads to altered hippocampal circuitry as well as learning and memory impairments. However, Berbel et al. (2010) demonstrated that these adverse effects during the third trimester can be ameliorated with prompt and sufficient maternal TH treatment.

Animal models of CH have typically examined TH deficiency in rats between gestational day 18 and postnatal day 21, which is roughly equivalent to the start of the third trimester until the first postnatal year in humans (see Figure 1.4). The results of these animal studies have shown that TH deficiency during this period impairs neurogenesis, synaptic function, and dendritic growth, particularly within the dentate gyrus (Gilbert & Paczowski, 2003; Gilbert & Sui, 2006; Rami, Patel, & Rabié, 1986). The dentate gyrus is an important relay zone for a unidirectional neural circuit known as the perforant path, which projects information from the neocortex to the dentate gyrus and CA fields and is thought to mediate episodic and spatial memory (see Figure 1.5 for a description of the perforant path; Bachevalier & Vargha-Khadem, 2005; Vago et al., 2007; Witter, 2007). Thus, damage to the dentate gyrus may have important
consequences for the development and organization of hippocampal neural circuits that are involved in episodic memory. Similar to animal models of HYPO, animal models of CH have also shown that this condition is associated with poor spatial learning and memory performance on water maze tasks (Reid, Kim, Page, O’Mara, & O’Hare, 2007). Interestingly, in a recent structural MRI study by Hasegawa, Kida, and Wada (2010), no specific volume reductions within the hippocampus were found in rats who received insufficient TH levels during late gestation. Given that a large portion of the hippocampus develops before the third trimester in humans (apart from the small dentate gyrus), Hasegawa et al. (2010) suggested that TH deficiency during the second trimester in humans may have a more significant impact on hippocampal volume than TH deficiency during the third trimester. Similarly, other studies examining adult-onset TH deficiency in rats have shown that the adult brain is less vulnerable to the structural damage caused by TH deficiency than the developing fetal brain (Madeira et al., 1992). However, numerous functional impairments in associative learning, spatial memory, and long-term potentiation are still evident in rats with adult-onset hypothyroidism (e.g., Alzoubi, Gerges, Aleisa, & Alkadhi, 2009; Fernández-Lamo, Montero-Pedrazuela, Delgado-Garcia, Guadano-Ferraz, & Gruart, 2009).

Overall, animal models of maternal and congenital hypothyroidism clearly indicate that the timing of TH deficiency can result in different structural impairments within the hippocampus. Early prenatal TH deficiency, particularly during the second and early third trimesters, appears to have the most significant impact on hippocampal structure because it impairs critical periods of neurogenesis and neuronal migration in the large CA1 field (Ausó et al., 2004; Berbel et al., 2010). In contrast, late prenatal and postnatal TH deficiency has been associated with impaired neurogenesis and synaptic function within the smaller dentate gyrus, which could lead to altered patterns of connectivity between hippocampal subregions (Gilbert & Paczowski, 2003; Gilbert & Sui, 2006). Importantly, animal models of HYPO and CH conditions
(i.e., pre- and postnatal TH deficiency) have both demonstrated impaired synaptic function within the hippocampus, as well as learning and memory deficits (Liu et al., 2010; Reid et al., 2007). According to Gilbert and Paczowski (2003), abnormal synaptic function and neural connectivity within the hippocampus likely contributes to the learning and memory impairments observed in TH-deficient populations. Given that the hippocampus functions as a network of neural connections rather than independent subregions (Small et al., 2001), both HYPO and CH conditions may be associated with poor episodic memory due to impaired synaptic transmission and altered neural circuitry within the hippocampus, despite the fact that these two conditions are associated with different patterns of structural damage within hippocampal subregions.

1.1.2 Maternal Hypothyroidism During Pregnancy and Associated Child Outcomes

Maternal hypothyroidism affects approximately 0.3-3% of all human pregnancies; however, no screening programs for maternal hypothyroidism in pregnant women currently exist, apart from those associated with experimental trials (Chan & Rovet, 2003; Glinoer & Spencer, 2010; Mitchell & Klein, 2004). Hypothyroidism during pregnancy is typically diagnosed using a thyroid stimulating hormone (TSH) test (Glinoer & Spencer, 2010). As shown in Figure 1.6, when TH levels are too low, the hypothalamus releases a hormone that stimulates the anterior pituitary gland to release thyroid stimulating hormone (TSH) and this in turn stimulates the thyroid gland to release more TH (Bernal & Nunez, 1995; Howdeshell, 2002; Koibuchi & Chin, 2000). In cases of hypothyroidism, however, a defect in the thyroid gland impairs the production of TH and causes an accumulation of TSH. According to Glinoer and Spencer (2010), the TSH test is the gold standard for diagnosing hypothyroidism because elevated TSH is often the most sensitive and reliable measure of thyroid function abnormalities. A diagnosis of hypothyroidism in non-pregnant individuals requires elevated TSH levels above the normal range of 0.4 to 4.1 mU/L, whereas in pregnant women, an elevated TSH level above 2.5 mU/L can signify
hypothyroidism (Glinoer & Spencer, 2010; Mandel, 2004). Unfortunately, TSH levels fluctuate dramatically over the course of a normal pregnancy, which can make the diagnosis and treatment of maternal hypothyroidism quite difficult (Glinoer & Spencer, 2010). In addition, research by Alexander et al. (2004) indicates that approximately 85% of pregnant hypothyroid women are inadequately treated during the first few months of pregnancy and typically require significantly higher doses of synthetic TH (i.e., by 50%) by midgestation. As a result, many offspring of treated hypothyroid women receive insufficient levels of maternal TH in the first half of gestation due to inadequate maternal TH treatment. Fortunately, these findings have been recently translated into a new set of guidelines for the management of maternal hypothyroidism during pregnancy (Abalovich et al., 2007; De Groot et al., in press).

Despite numerous animal studies showing that maternal TH deficiency is associated with abnormal hippocampal development and memory impairments in offspring, very few studies have examined memory performance and no study has investigated hippocampal structure (e.g., volumes) in children of hypothyroid women. Nevertheless, several studies have found deficits in intelligence, attention, visuospatial skills, fine motor skills, and language in offspring of untreated hypothyroid women (Haddow et al., 1999; Man, Brown, & Serunian, 1991; Pop et al., 1999). In cases of treated maternal hypothyroidism during pregnancy, one study found no adverse effects on IQ scores in the offspring (Liu et al., 1994). In contrast, other studies have continued to observe abnormalities in visuospatial skills, infant mental development, and attention in offspring of treated hypothyroid women, especially when the mothers received inadequate doses of synthetic TH during the first half of pregnancy (Haddow et al., 1999; Man et al., 1991; Mirabella, Feig, Astzalos, Perlman, & Rovet, 2000; Mirabella et al., 2005; Pacaud et al., 1995; Smit et al., 2000). Overall, visuospatial impairments appear to be the most prominent weakness reported in children of treated hypothyroid women, possibly because the second trimester is also a sensitive period for the developing visual cortex, which also requires TH for
proper neurodevelopment (Man et al., 1991; Mirabella et al., 2005). However, given that few studies have directly assessed memory function in this population, it is also possible that children of hypothyroid women could exhibit weaknesses in episodic AM due to the adverse affects of early prenatal TH deficiency on hippocampal structure and function.

1.1.3 Congenital Hypothyroidism and Associated Child Outcomes

Congenital hypothyroidism (CH) is a condition of fetal thyroid dysfunction that affects approximately 1 in 2500 newborns (Harris & Pass, 2007). The three most common etiologies of CH are: (a) athyrosis, referring to an absent or dysfunctional thyroid gland; (b) ectopic or lingual, referring to an abnormally located thyroid gland; and (c) dyshormonogenesis, referring to a defect in TH synthesis (Hanukoglu et al., 2001). In many cases of CH, particularly those with athyrosis, the period of TH deficiency begins early in the third trimester because the fetal thyroid gland is unable to produce enough TH to supplement the declining maternal contribution of TH (see Figure 1.2a; Rovet & Daneman, 2003). Without treatment, CH can cause severe brain damage and mental retardation, resulting in a syndrome known as cretinism (Chen & Hetzel, 2010). Over the past 30 years, however, screening programs that identify CH in newborns and allow for immediate treatment of those with elevated TSH levels have resulted in significantly reduced severity of the deficits previously observed in this population (Rovet, 2005).

Nevertheless, several studies have reported that children with early-treated CH (i.e., treatment within the first two weeks after birth) continue to exhibit mild cognitive deficits, particularly in intelligence, episodic memory, visuospatial memory, attention, and learning (Bargagna et al., 2000; Derksen-Lubsen & Verkerk, 1996; Dimitropoulos et al., 2009; Kempers et al., 2006; Oerbeck, Sundet, Kase, & Heyerdahl, 2005; Rovet, Ehrlich, & Sorbara, 1992; Rovet, 1999; Song, Daneman, & Rovet, 2001). In addition, the only study so far to investigate hippocampal structure in children who experienced early TH deficiency using structural MRI revealed
significantly reduced left hippocampal volumes in children with early-treated CH relative to typically developing controls (Wheeler, Willoughby, McAndrews, & Rovet, 2011).

While the structural and functional deficits observed in children with CH are most likely associated with their untreated exposure to TH deficiency during late gestation (i.e., the third trimester) and first few weeks of life, research suggests that due to poor management and treatment of CH, many children with CH also experience prolonged periods of mild TH deficiency throughout infancy and childhood (Heyerdahl & Kase, 1995). Children with CH who experienced longer postnatal periods of TH deficiency due to inadequate TH treatment, exhibit poorer memory, visuospatial, and attention abilities than those who experienced shorter postnatal periods of TH deficiency (Rovet et al., 1992; Selva, Harper, Downs, Blasco, & LaFranchi, 2005; Song et al., 2001). In addition, several studies have reported that many children receiving treatment for CH continue to exhibit abnormally elevated TSH levels during childhood due to insufficient doses of synthetic TH (Abusrewil, Tyfield, & Savage, 1988; Hanukoglu et al., 2001; Heyerdahl & Kase, 1995; Rovet, 1999). Thus, despite receiving TH treatment, many children with CH are exposed to mild TH deficiency throughout childhood, which may also have important consequences for their hippocampal development and cognitive performance.

Unlike the literature on offspring of hypothyroid women, significant research has been conducted on memory functioning in children with CH. Previous studies from our lab have shown that children with CH show impairments in both verbal episodic memory (i.e., story recall) and delayed visuospatial memory, with more severe deficits found in those with an athyrosis etiology (Rovet, 1999; Rovet et al., 1992; Rovet & Ehrlich, 2000; Song et al., 2001; Wheeler et al., 2011). Oerbeck et al. (2005) also found deficits in verbal episodic memory and delayed visual memory in young adults with CH relative to sibling controls. According to Song et al. (2001), late prenatal periods of TH deficiency appear to have the most significant impact on visuospatial and perceptual abilities, whereas memory abilities appear to be influenced primarily
by postnatal periods of TH deficiency. However, direct comparisons of HYPO and CH conditions are required in order to investigate how the timing of early TH deficiency specifically affects memory and visuospatial abilities.

1.1.4 Summary and Model of Early Thyroid Hormone Deficiency

Animal models of HYPO and CH have provided important insight into how the timing of early TH deficiency affects hippocampal structure. The evidence to date indicates that early prenatal TH deficiency (or HYPO) primarily affects the large CA1 field, whereas late prenatal and postnatal TH deficiency (or CH) primarily affects the smaller dentate gyrus (Ausó et al., 2004; Gilbert & Paczowski, 2003). Given that early prenatal TH deficiency in rats is associated with the most significant alterations in hippocampal structure (Lavado-Autric et al., 2003), it is possible that children of treated hypothyroid women may exhibit greater reductions in hippocampal volume than those previously observed in children with early-treated CH (i.e., in Wheeler et al., 2011).

In terms of hippocampal function, animal models have shown that both HYPO and CH conditions are associated with impaired synaptic functioning and memory deficits, irrespective of different structural abnormalities within the hippocampus (Liu et al., 2010; Reid et al., 2007). This finding suggests that both the CA1 field and dentate gyrus, or the neural circuits that connect these two subregions, play an important role in episodic memory because disrupted synaptic function in either of these hippocampal subregions results in learning and memory deficits in rats (Gilbert & Sui, 2006; Liu et al., 2010; Reid et al., 2007). Consequently, both HYPO and CH groups may exhibit abnormal hippocampal activation during memory retrieval tasks relative to controls, due to alterations in neuronal migration, neural connectivity, and synaptic functioning. Given the paucity of human studies examining memory performance in HYPO and the fact that no study has yet examined episodic AM in individuals with TH
deficiency, it is unclear whether both HYPO and CH groups will exhibit weaknesses in episodic AM. However, children with early-treated CH exhibit poor verbal episodic memory and both HYPO and CH groups show similar impairments in visuospatial abilities (Man et al., 1991; Mirabella et al., 2005; Oerbeck et al., 2005; Rovet, 1999). Thus, both HYPO and CH groups may exhibit poor episodic AM recall, with a particular weakness in recalling visuospatial details.

1.2 Overview of Autobiographical Memory

Autobiographical memory (AM), or the recollection of personally experienced past events, is a multifaceted higher-order cognitive process that includes both episodic and semantic memory components (Levine, Svoboda, Hay, Winocur, & Moscovitch, 2002; Tulving, 2002). Episodic AM refers to remembering specific past events and involves the recollection of vivid sensory, perceptual, and emotional details (e.g., one’s 16th birthday; Addis, Moscovitch, Crawley, & McAndrews, 2004; St-Laurent, Moscovitch, Levine, & McAndrews, 2009; Tulving, 2002). In contrast, semantic AM refers to the recollection of personal facts, traits, or general self-knowledge, independent of any sense of re-experiencing a past event (e.g., the name of one’s high school; Levine et al., 2002; Tulving, 2002). One critical component of episodic AM, which differentiates it from semantic AM and other forms of declarative memory, is the requirement of autonoetic consciousness or the ability to re-experience one’s prior conscious experience of an event at time of recollection (Tulving, 2002; Wheeler, Stuss, & Tulving, 1997). A second important aspect of episodic AM retrieval is that it often involves visuospatial imagery because the visualization of unique visual, spatial, and perceptual details can significantly enhance the ability to re-experience past events (Gilboa, Winocur, Grady, Hevenor, & Moscovitch, 2004; Rubin & Greenberg, 1998).

Episodic AM and semantic AM are highly interconnected, especially during the early stages of retrieval when personal semantic knowledge can aid memory search and retrieval.
operations (Conway & Pleydell-Pearce, 2000; Svoboda, McKinnon, & Levine, 2006). However, recent research suggests that these two forms of AM can be differentiated, not only by their distinct properties, but also by their developmental trajectories (Piolino et al., 2007) and their underlying neural activations (Maguire & Mummery, 1999). For example, Piolino et al. (2007) recently showed that episodic AM is associated with a later and more gradual developmental trajectory across childhood than semantic AM. Neuroimaging studies in adults have also shown that episodic AM retrieval tends to activate the hippocampus and parahippocampal gyrus to a greater extent than semantic AM retrieval (Hoscheidt et al., 2010; Maguire & Mummery, 1999). In addition, adult patients with hippocampal damage exhibit impairments in episodic AM, but not semantic AM, suggesting that the hippocampus plays a more critical role in episodic AM than in semantic AM (Noulhiane et al., 2007; Steinvorth, Levine, & Corkin, 2005; St-Laurent et al., 2009; Viskontas, McAndrews, & Moscovitch, 2000). Despite an extensive literature investigating AM in adults, few studies have examined both episodic and semantic AM in children, especially those with abnormal hippocampal development. In addition, no study has yet used functional MRI to investigate hippocampal activation during episodic and semantic AM retrieval in either typically developing children or children with hippocampal abnormalities.

1.2.1 Episodic and Semantic AM in Typically Developing Children

While the emergence of semantic AM in young children has not been specifically examined, some evidence does exist suggesting that young children exhibit semantic AM prior to demonstrating episodic AM and autonoetic consciousness (Tulving, 2002). For example, preschool children are able to remember specific facts about past events (e.g., a school trip) even after lengthy delays (Fivush & Hammond, 1990). However, this event knowledge is mostly semantic, fragmentary, and heavily dependent on the provision of retrieval cues or prompting questions by adults (Fivush & Hammond, 1990; Newcombe, Lloyd, & Ratcliff, 2007).
Importantly, young children (i.e., under four years of age) do not appear to spontaneously recall or truly re-experience specific past events, which are necessary components of episodic AM retrieval (Newcombe et al., 2007; Perner & Ruffman, 1995).

The apparent absence of episodic AM during the first two years of life (i.e., the period reflecting ‘infantile amnesia’) is thought to be due to immature hippocampal functioning, particularly poor encoding and storage of details associated with specific events (Bauer, 2006; Newcombe et al., 2007). According to Bachevalier and Vargha-Khadem (2005), most abilities that depend on the hippocampus, such as episodic AM, emerge late in development because the hippocampus continues to grow during the first two years of life and has substantial postnatal maturation. Thus, a hierarchical model of AM has been proposed with semantic AM developing early and providing a foundation for the later and more gradual development of episodic AM (Mishkin, Suzuki, Gadian, & Vargha-Khadem, 1997).

Early investigations of the emergence of episodic AM relied primarily on retrospective data in adults demonstrating that their earliest AMs tended to cluster around the ages of 3 and 4 (Bruce, Dolan, & Phillips-Grant, 2000; Rubin, 2000). Based on these findings, the term ‘childhood amnesia’ was created to describe a period of impoverished episodic AM that gradually improves between the ages of 3 and 5 (Newcombe et al., 2007). As more sophisticated experimental designs for investigating AM were developed, converging lines of evidence indicated that the emergence of episodic AM was associated with: (a) improvements in basic memory processes, such as encoding, storage, and retrieval (Hudson & Fivush, 1991); (b) advances in higher-order cognitive processes that facilitate episodic AM, such as language, self-awareness, and theory of mind (Howe, Courage, & Edison, 2003; Klein, German, Cosmides, & Gabriel, 2004; Perner & Ruffman, 1995); and (c) maturation of requisite brain regions and neural networks involved in episodic AM, particularly the hippocampus and prefrontal cortex (Gogtay et al., 2006; Ofen et al., 2007; Wheeler et al., 1997). Similar to the hippocampus, the prefrontal
cortex has been identified as a critical region for AM retrieval because it controls self-referential processing (i.e., processing personal information), as well as memory search, retrieval, and evaluation processes, through its interactions with the hippocampus and medial temporal lobe (Buckner & Wheeler, 2001; Cabeza et al., 2004).

Despite an extensive literature on the emergence of episodic AM in young children, only two studies to date have examined age-related differences in both episodic and semantic AM beyond the age of 5. The first study by Piolino et al. (2007) used an adapted version of the Autobiographical Memory Interview (AMI; Kopelman, Wilson, & Baddeley, 1989) and Tulving’s (1985) Remember/Know Paradigm to examine age-related differences in episodic and semantic AM, as well as autonoetic consciousness, during childhood. The results indicated that between the ages of 7 and 13 years, significant age-related improvements are observed in recollecting and re-experiencing specific childhood events, whereas semantic AM (e.g., recalling names of childhood friends) shows no significant change with age (Piolino et al., 2007). Importantly, this study was the first to demonstrate that episodic AM develops over a prolonged period that extends well beyond the offset of childhood amnesia (i.e., around age 5).

In a second more refined study, Piolino and colleagues found significant improvements in both episodic and semantic AM across childhood and thus concluded that increases in semantic AM across childhood facilitate the development of episodic AM (Picard, Reffuveille, Eustache, & Piolino, 2009). In addition, age-related improvements in episodic AM were found to be associated with parallel improvements in verbal episodic memory (i.e., story recall), semantic AM, and executive functioning (Picard et al., 2009). These findings suggest that the development of episodic AM corresponds to the development of other cognitive abilities, including those that rely on the hippocampus (e.g., episodic memory) and prefrontal cortex (e.g., executive functioning; Picard et al., 2009). Given that the hippocampus and prefrontal cortex both exhibit prolonged structural and functional maturation during childhood and adolescence (Benes, Turtle,
Khan, & Farol, 1994; Grieve, Korgaonkar, Clark, & Williams, 2011; Huttenlocher & Dabholkar, 1997; Lenroot & Giedd, 2006), episodic AM may continue to develop during adolescence due to improved neural connectivity between the hippocampus, prefrontal cortex, and other core regions of the AM neural network. However, additional investigations into the development of episodic AM across both childhood and adolescence are required to examine this issue further.

1.2.2 Episodic and Semantic AM in Patients With Hippocampal Damage

Research on the effects of hippocampal damage on subsequent memory performance has provided an important avenue for investigating the role of the hippocampus in episodic and semantic AM. For example, Vargha-Khadem and colleagues have examined episodic and semantic memory performance in children, adolescents, and young adults with developmental amnesia, which is a condition characterized by selective bilateral damage to the hippocampus (i.e., a 20-50% reduction in hippocampal volume) due to a brief periods of hypoxic ischemia (i.e., a lack of oxygen to the brain; Vargha-Khadem et al., 1997; 2003). These patients showed deficits in episodic AM, verbal episodic memory (i.e., story recall), delayed visuospatial memory, and everyday memory, but had preserved semantic memory (de Haan, Mishkin, Baldeweg, & Vargha-Khadem, 2006; Gadian et al., 2000; Maguire, Vargha-Khadem, & Mishkin, 2001; Vargha-Khadem et al., 1997; 2003). Interestingly, de Haan et al. (2006) noted that the episodic memory impairments exhibited by this group of patients were not apparent until late childhood, thus lending support to the hierarchical model of AM development because their impaired episodic AM appears to have developed later than their intact semantic memory. One of the patients (i.e., patient Jon) who sustained hippocampal damage very early in life was also studied by Maguire et al. (2001) using functional MRI. Maguire et al. (2001) found that patient Jon showed abnormal patterns of hippocampal activity during episodic AM retrieval relative to controls. In particular, Jon showed bilateral hippocampal activation, rather than the left-
lateralized pattern observed in controls, as well as altered neural connectivity between the
hippocampus and other regions within the AM neural network (Maguire et al., 2001).

Overall, studies of patients with developmental amnesia indicate that severe hippocampal
damage results in impairments in episodic AM and delayed visuospatial memory and these
impairments appear to be associated with significant alterations in patterns of hippocampal
activation during episodic AM retrieval (Maguire et al., 2001; Vargha-Khadem et al., 1997).
Vargha-Khadem et al.’s (1997) study was instrumental in showing that verbal episodic memory,
delayed visuospatial memory, and everyday memory are critically dependent on the
hippocampus, whereas semantic memory appears to be relatively unaffected by early
hippocampal damage. Although it is unclear which hippocampal subregions are specifically
affected in patients with developmental amnesia, a case study of a patient who experienced an
ischemic episode at age 52 showed that hypoxic ischemia resulted in selective bilateral damage
to the entire CA1 field of the hippocampus (i.e., evident in an autopsy five years later; Zola-
Morgan, Squire, & Amaral, 1986). Importantly, this patient had earlier shown a similar pattern of
deficits as individuals with developmental amnesia, including impaired episodic memory (i.e.,
story recall and recall of recent AMs) and poor delayed visuospatial memory, but preserved
semantic memory (Zola-Morgan et al., 1986). Thus, severe damage to the CA1 field in humans
appears to be associated with significant impairments in episodic AM and visuospatial memory.

Studies of patients with temporal lobe epilepsy have shown that damage to the
hippocampus later in life is also associated with significant impairments in episodic AM, verbal
episodic memory (e.g., word list recall), and delayed visuospatial memory, but relatively intact
semantic AM and general semantic memory (Noulhiane et al., 2007; Viskontas et al., 2000).
Temporal lobe epilepsy has been linked to significant cellular damage in both the CA1 field and
dentate gyrus, as severe seizures occurring early in life can significantly alter neural circuitry
within the hippocampus (Houser, 1990; Velez-Pardo et al., 2004). Interestingly, St-Laurent et al.
(2009) recently used Levine et al.’s (2002) Autobiographical Interview to demonstrate that patients with left or right temporal lobe epilepsy or temporal lobe excision were particularly impaired in recalling perceptual details (e.g., visual details) from specific past events. This finding suggests that the hippocampus may play an important role in retrieving visual/perceptual details through visual imagery and rich perceptual re-experiencing of past events, which are two critical components of episodic AM retrieval (Gilboa et al., 2004; Rubin & Greenberg, 1998). In addition, Noulhiane et al. (2007) recently used Tulving’s (1985) Remember/Know Paradigm to demonstrate impaired autonoetic consciousness (i.e., poor re-experiencing of past events at the time of recollection) in patients with left or right temporal lobe epilepsy and medial temporal lobe resections.

Finally, a functional MRI study by Addis, Moscovitch, and McAndrews (2007) showed that during episodic AM retrieval, patients with left temporal lobe epilepsy and significant left hippocampal atrophy showed reduced hippocampal activation, as well as altered effective connectivity within the AM neural network, relative to controls. These findings indicate that unilateral hippocampal damage sustained later in life significantly impairs functional organization and connectivity within the AM neural network, albeit in a slightly different way than patient Jon’s bilateral hippocampal damage sustained very early in life (i.e., at birth). To our knowledge, no study has yet examined episodic AM in children with temporal lobe epilepsy. However, several studies investigating other forms of memory in this clinical pediatric population have shown that these children exhibit similar deficits in verbal episodic memory (i.e., story recall), delayed visuospatial memory, and everyday memory as those observed in children with early TH deficiency and individuals with developmental amnesia (Gonzalez, Anderson, Wood, Mitchell, & Harvey, 2007; Jambaqué et al., 2007; Kadis, Stollstorff, Elliott, Lach, & Smith, 2004; Mabbot & Smith, 2003). Overall, converging evidence suggests that episodic AM and delayed visuospatial memory impairments are hallmark deficits in patients who
sustained hippocampal damage very early in life. In addition, Maguire et al.’s (2001) study revealed that a patient with early hippocampal damage also exhibited abnormal patterns of hippocampal activation during episodic AM retrieval, suggesting that functional reorganization and neural compensation may occur in the context of very early hippocampal damage.

1.2.3 Functional Neuroanatomy of AM retrieval and the Essential Role of the Hippocampus

In the majority of functional MRI studies investigating AM retrieval in adults, a core neural network of left-lateralized brain regions involved in memory retrieval, self-referential processing, and visuospatial processing has been described (see Svoboda et al., 2006 for a review). The core regions of the AM neural network include the hippocampus, parahippocampal gyrus, medial and ventrolateral prefrontal cortices, anterior cingulate, retrosplenial and posterior cingulate cortices, temporoparietal junction, lateral temporal regions, and cerebellum (see Figure 1.7; Svoboda et al., 2006). The left lateralized pattern of activity within core regions of the AM neural network, however, has not always been consistently observed. For example, several studies have shown bilateral activation of these regions (e.g., the hippocampus) during AM retrieval, especially when participants are given more time to retrieve, visualize, and re-experience past events (Addis et al., 2004; Cabeza et al., 2004; Gilboa et al., 2004; Ryan et al., 2001; Viard et al., 2007). According to Conway, Pleydell-Pearce, Whitecross, & Sharpe (2002), the left-lateralized pattern of activation during AM retrieval may reflect initial stages of memory search and retrieval processes that often involve semantic AM, whereas later activation within the right hemisphere may reflect the process of re-experiencing and visualizing past events. However, there does appear to be a left hemisphere bias within the AM neural network in young adults given that stronger left-than-right activations have been reported during episodic AM retrieval (Maguire & Mummery, 1999).
Although many different brain regions are involved in AM retrieval, the hippocampus plays an essential role because it is necessary for the retrieval of contextual and visuospatial details of past events (Eldridge et al., 2000; Gilboa et al., 2004; Maguire et al., 2001; Moscovitch et al., 2005). Studies specifically contrasting episodic and semantic AM retrieval have found greater activation within the hippocampus during the recollection of specific past events than during the recollection of personal semantic information (e.g., Maguire & Mummery, 1999; Svoboda & Levine, 2009). This finding is supported by the multiple-trace theory, which predicts that episodic AM encoding and retrieval is critically dependent on the hippocampus, whereas semantic AM can be mediated by extra-hippocampal structures (Nadel & Moscovitch, 1997). For example, semantic AM is thought to be largely controlled by other regions within the temporal lobe, such as the temporal pole, middle temporal gyrus, and perirhinal cortex, because patients with damage to these regions exhibit deficits in semantic memory (Davies, Graham, Xuereb, Williams, & Hodges, 2004; Mummery et al., 2000). Finally, functional MRI studies have also shown that greater activation of the hippocampus during episodic AM retrieval is associated with more vivid re-experiencing of past events, providing further evidence that the hippocampus is critical for episodic AM and autonoetic consciousness (Addis et al., 2004; Gilboa et al., 2004).

Although numerous fMRI studies have investigated episodic and semantic AM retrieval in adults, no study has yet investigated hippocampal activation during AM retrieval in typically developing children. Thus, it remains unclear whether children will show similar or different patterns of hippocampal activation during episodic and semantic AM retrieval compared to those observed in adults. In addition, no study has examined hippocampal activity during episodic and semantic AM retrieval in children with hippocampal abnormalities. Based on Maguire et al.’s (2001) findings from a young adult with developmental amnesia who sustained hippocampal damage very early in life, it could be possible that children with early TH deficiency may also exhibit greater bilateral recruitment of the hippocampus during episodic AM retrieval, but not
during semantic AM retrieval, than controls in order to compensate for abnormalities in hippocampal structure and function. Thus, fMRI research is clearly needed in order examine hippocampal function during AM retrieval in both typically and atypically developing children.

1.3 Objectives of the Present Research

The main goal of the present research is to investigate episodic and semantic AM performance, as well as hippocampal structure and function, in children with early TH deficiency relative to typically developing controls. Given that no single measure of both episodic and semantic AM was available for the investigation of AM performance in children, it was first necessary to develop and evaluate the Children’s Autobiographical Interview (CAI), a new child-friendly version of Levine et al.’s (2002) Autobiographical Interview for adults. In order to validate the use of this tool for clinical pediatric populations, this dissertation begins with a normative study of episodic and semantic AM performance in typically developing children and adolescents. What follows are three studies investigating episodic and semantic AM using the CAI, as well as hippocampal structure and function using MRI, in children with early TH deficiency and typically developing controls. Overall, this dissertation includes four studies that seek to address the following five aims: (1) to investigate episodic and semantic AM in a large sample of typically developing children and adolescents in Study I; (2) to compare episodic and semantic AM recall in children with early TH deficiency to controls in Study II; (3) to investigate episodic AM accuracy using a staged event in children with early TH deficiency and controls in Study III; (4) to examine whether children with early TH deficiency exhibit reduced hippocampal volumes relative to controls and whether hippocampal volumes are associated with episodic AM recall and/or accuracy performance in Studies II and III; (5) to examine hippocampal activation during episodic and semantic AM retrieval in children with early TH deficiency and controls in Study IV.
The thyroid gland releases two thyroid hormones, thyroxine (T4) and triiodothyronine (T3), into the bloodstream where they travel to the brain. T4, which is the most abundant form of TH, is able to cross the blood-brain barrier and enter an astrocyte, where it is converted to T3 (i.e., the bioactive form of TH) via the action of type-II deiodinase enzyme (D2). T3 is then transported into a neuron where it binds to a TH receptor (TR) and activates the transcription of genes that influence neurogenesis, neuronal migration, myelination, synaptogenesis, and dendritic and axonal growth (Bernal & Nunez, 1995). This figure is adapted from Santisteban & Bernal (2005) with permission from Springer®.
Figure 1.2

Estimated Timeline Illustrating the Source of Thyroid Hormones (TH) During Gestation (a) and Key Neurodevelopmental Events Within the Cortex and Hippocampus (b) from Conception to 6 Months of Life

The top panel (a) shows maternal (solid) and fetal (dashed) thyroxine (T4) contributions throughout gestation and in the first few months after birth. The fetal thyroid gland develops in the first trimester and begins to produce TH in the middle of the second trimester. The bottom panel (b) provides an estimation of major neurodevelopmental events within the cortex and hippocampus and outlines critical periods for the CA1-4 fields and dentate gyrus during gestation (Berbel, Guadano-Ferraz, Angulo, & Ramón Cerezo, 1994, Howdeshell, 2002). This figure is adapted from Williams (2008) with permission from Blackwell Publishing LTD© and Howdeshell (2002) with permission from Environmental Health Perspectives© (available at: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1241181/pdf/ehp110s-000337.pdf).
The CA fields and dentate gyrus (DG) are two u-shaped inter-locking layers that are evident along the entire longitudinal axis of the hippocampus (i.e., hippocampal head, body, and tail). The CA1 field comprises the largest portion of the hippocampus (65%), whereas the DG comprises the smallest portion of the hippocampus (5%; Harding et al., 1998). In addition, the CA1 field is the first subregion to develop during gestation, followed in succession by CA2, CA3, CA4, and finally the dentate gyrus, which has substantial postnatal maturation (Arnold & Trojanowski, 1996; Seress et al., 2001). This figure is adapted with kind permission from Springer Science + Business Media©: “The Human Hippocampus: Functional Anatomy, Vascularization and Serial Sections with MRI” Third Edition, 2005, Henri M. Duvernoy, Figures 7A and 21.
Gestational day 10 to GD18 is roughly equivalent to the second trimester in humans, GD18 to PND6 is roughly equivalent to the third trimester in humans, and PND6 to PND 20 is roughly equivalent to the first year of life in humans (Berbel et al., 1994; Howdeshell, 2002). This figure is adapted from Howdeshell (2002) with permission from Environmental Health Perspectives© (available at: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1241181/pdf/ehp110s-000337.pdf).
The unidirectional perforant pathway (black line), also known as the trisynaptic circuit, is thought to be involved in episodic AM and spatial memory (Vago et al., 2007; Witter, 2007). Its major cortical inputs are the parietal association cortex (BA7) via the parahippocampal gyrus as well as the temporoparietal junction (BA39/40/22). Information from these regions enters the entorhinal cortex and travels consecutively through the subiculum, dentate gyrus, and CA fields. The major outputs of the perforant path are the thalamus (via the fornix) and regions that control visuospatial processing, such as the posterior cingulate (BA23) and the retrosplenial cortex (BA29/30). The direct pathway (gray line), or temporoammonic pathway, involves a loop between the entorhinal cortex, CA1 field, and subiculum and is also thought to play an important role in memory retrieval (Vago et al., 2007).
When TH levels are low, the hypothalamus responds by releasing thyrotropin-releasing hormone (TRH), which stimulates the anterior pituitary gland to release thyroid stimulating hormone (TSH) into the bloodstream. TSH then travels to the thyroid gland at the base of the neck, where it stimulates the release of the two THs, thyroxine (T4) and triiodothyronine (T3), into the bloodstream until their levels return to normal. When TH levels are high, however, the hypothalamic-pituitary-thyroid axis becomes down-regulated and TH production is inhibited. This complex and highly-regulated negative feedback system ensures that the fetal brain receives an adequate supply of maternal TH during critical periods of early brain development. In cases of hypothyroidism, however, a defect in the thyroid gland impairs the production of TH, causing an accumulation of TSH within the bloodstream (Rovet & Willoughby, 2010).
Figure 1.7


Activations in core (white), secondary (black), and infrequent (gray with a black border) regions of the AM neural network are shown across right (left column) and left (right column) lateral, medial, and subcortical sagittal planes. Both the right hippocampus (black circle of panel e) and left hippocampus (black circle of panel f) were reported as core regions of the AM neural network. This figure is reprinted from Svoboda et al. (2006) with permission from Pergamon©.
Chapter 2
Study I: Episodic and Semantic Autobiographical Memory and Everyday Memory in Typically Developing Children and Adolescents

2.1 Introduction

Autobiographical memory (AM) includes two primary components: episodic AM, which involves remembering specific past events, and semantic AM, which involves remembering personal facts. Evidence from developmental studies of AM suggests that these two forms of AM emerge at different rates, with semantic AM developing earlier and providing a foundation for the prolonged development of episodic AM (Picard et al., 2009; Piolino et al., 2007; Tulving, 2002). Despite an extensive literature on the emergence of episodic AM in young children, only two studies have examined age-related differences in both episodic and semantic AM beyond the age of 5. For example, Piolino et al. (2007) examined episodic and semantic AM in 42 children between the ages of 7 and 13 using the TEMPAu task (Test Episodique de Mémoire du Passé Autobiographique), an adapted version of Kopelman et al.’s (1989) Autobiographical Memory Interview. The TEMPAu task assesses children’s ability to recollect specific personal events (e.g., a school event, trip or vacation, and a family event) from three different time periods (e.g., current school year, last school year, and previous school years; Piolino et al., 2007). Results from Piolino et al.’s (2007) study revealed significant age-related improvements in episodic AM, but no significant differences in semantic AM (e.g., recalling names of childhood friends) across childhood. In addition, Piolino et al. (2007) used Tulving’s (1985) Remember/Know paradigm to demonstrate age-related improvements in autonoetic consciousness (i.e., ability to consciously re-experience past events at the time of recollection), as older children reported significantly more ‘Remember’ responses when judging their ability to truly remember and re-experience past events than younger children. Importantly, this study was the first to demonstrate that episodic AM continues to develop throughout childhood, well beyond the offset of childhood amnesia.
In a more recent study by the same research team, the TEMPAu task was again employed to examine episodic and semantic AM in 30 children between 6 and 11 years of age (Picard et al., 2009). The results indicated that age-related improvements in episodic AM across childhood correspond with age-related improvements in semantic AM, verbal episodic memory, and executive functioning (Picard et al., 2009). Contrary to their previous study, however, Picard et al. (2009) now observed that both episodic and semantic AM improved with age. Although Picard et al. (2009) did not account for this discrepancy from Piolino et al.'s (2007) study, their conflicting results may be due to the use of different statistical analyses for examining age effects across the two studies. For example, Piolino et al. (2007) stratified their sample into only three age groups (e.g., 7-8, 9-10, and 11-13) using ANOVA, whereas Picard et al. (2009) used age as a continuous variable in a regression analysis, which likely provided a more sensitive measure of age-related differences in semantic AM. Based on their results, Picard et al. (2009) concluded that having a more developed and extensive personal semantic knowledge base earlier in childhood supports and facilitates the development of episodic AM.

While Piolino et al.'s (2007) and Picard et al.'s (2009) studies provide informative data on episodic and semantic AM across childhood, their assessment of episodic and semantic AM was based on separate tasks, which were not matched for psychometric properties. For example, episodic AM was measured using the TEMPAu task, in which examiners provided subjective ratings (i.e., on a 4-point scale) of the overall specificity of participants’ recollections of specific childhood events (Piolino et al., 2007). In contrast, semantic AM was measured using a questionnaire, which required participants to list personal facts (e.g., childhood heroes, home address, names of friends, and hobbies) that were from the same time period (e.g., last school year) but may not have necessarily overlapped with event memory (Piolino et al., 2007; Rosenbaum et al., 2011). Consequently, it may be difficult to make direct comparisons of age-related differences in episodic and semantic AM from these two studies due to possible task-
related confounds (Levine, 2004). Given that episodic AMs are often embedded within a semantic context that links episodic AM details with personal facts, extended events, and lifetime periods (Svoboda et al., 2006), it would be particularly informative to examine whether the number of episodic and semantic AM details recalled within a single autobiographical narrative differs across childhood and adolescence. Thus, further replication of these studies using a more objective measure of AM that effectively dissociates episodic AM from semantic AM within a single task is warranted.

Given the paucity of studies examining AM beyond early childhood, the primary goal of the current study was to collect normative data on episodic and semantic AM across childhood and adolescence using the Children’s Autobiographical Interview (CAI), a new child-friendly version of Levine et al.’s (2002) Autobiographical Interview. In contrast to Piolino et al.’s (2007) TEMPAu task, the CAI: (a) effectively dissociates episodic and semantic AM within a single autobiographical narrative, (b) provides an objective and reliable measure of episodic AM (i.e., total number of details recalled), which can be subdivided into specific subcategories of details (e.g., event, time, place, perceptual, and emotion/thought); (c) incorporates a standardized qualitative rating system as an additional measure of episodic re-experiencing that is comparable to the rating system used in the TEMPAu task, and (d) allows for the examination of different levels of retrieval support (Levine et al., 2002). Although the Autobiographical Interview has been used extensively to examine episodic and semantic AM in healthy young adults, older adults, and patients with hippocampal damage (Addis et al., 2007; Levine et al., 2002; Rosenbaum et al., 2011; Steinvorth et al., 2005; St-Laurent et al., 2009), it has not yet been used to examine AM performance in children or adolescents. Thus, the normative data reported in the present study will provide an important reference for future studies that use the CAI to explore episodic and semantic AM in atypically developing pediatric populations. Because the main purpose of the present study was to examine age-related differences in AM across both
childhood and adolescence, the age groups from Piolino et al.’s (2007) and Picard et al.’s (2009) studies were extended to include adolescents up to 16 years of age. It was hypothesized that while episodic and semantic AM would both improve across childhood and adolescence, there would be greater age-related improvements in episodic AM than semantic AM.

Given that Picard et al. (2009) showed parallel improvements between episodic AM and several other cognitive functions (i.e., semantic AM, verbal episodic memory, and executive functioning) across childhood, a secondary goal of the present study was to examine whether similar age-related increases were evident between episodic AM and everyday memory.

Everyday memory, as measured by the Everyday Memory Questionnaire (EMQ; Sunderland et al., 1983), reflects one’s ability to perform real-world memory tasks within various domains, such as remembering faces, places, and actions/tasks. Similar to episodic AM, everyday memory is thought to be critically dependent on the hippocampus because patients who sustained either mild or severe hippocampal damage early in life exhibit significant deficits in everyday memory on the EMQ (Isaacs et al., 2000, Vargha-Khadem et al., 1997). To our knowledge, no study has specifically compared episodic AM and everyday memory ability in typically developing children. Based on Picard et al.’s (2009) findings, it was hypothesized that similar age-related improvements would be found between episodic AM and everyday memory in typically developing children and adolescents.

2.2 Methods

2.2.1 Participants

Two hundred and twenty-three typically developing children and adolescents (52% male) between 8-16 years of age ($M = 11.80, SD = 2.55$) were recruited for the present study while visiting the Ontario Science Centre in Toronto, Canada. Exclusionary criteria included a diagnosis of attention-deficit hyperactivity disorder (ADHD), an identified learning disability, a psychiatric disorder, a head injury resulting in a loss of consciousness, and a debilitating or
chronic medical condition. As a result, 17 participants were excluded for having ADHD and eight for having a learning disability. In addition, 16 participants were unable to recall two specific AMs (e.g., they described a week-long event) and so their data were excluded from the analyses (note: these cases were equally distributed across age groups). Thus, the remaining sample of participants consisted of 182 children and adolescents (48% male) between 8 and 16 years of age ($M = 11.88, SD = 2.55$). The distribution of participants by age and sex is reported in Table 2.1.

The majority of participants were Caucasian (68%) with the remainder being Chinese (12%), South Asian (8%), Multi-ethnic (7%), Middle Eastern (2%), African American (2%), and Latino (1%). English was the primary language spoken in all homes; however, 14% of participants were also fluent in a second language (e.g., Chinese, Arabic, Greek, or Tamil). Socioeconomic status (SES) of each participant was computed using the Hollingshead Four-Factor Index (Hollingshead, 1975) based on parental occupation and education. This score was calculated for each participant by averaging SES scores of both parents (or using only one parent’s score when this was the only information available). Across all participants, family Hollingshead SES scores ranged from 25 to 66 ($M = 48.70, SD = 10.67$) and included 3% in the medium-low income range, 22% in the medium income range, 40% in the medium-high income range, and 35% in the high income range.

### 2.2.2 General Procedure

All parents or guardians provided written consent for participation in this study while participants also provided verbal assent. Interviews were conducted on eight successive weekends over a two-month period. Participants were interviewed individually for approximately 20 minutes in an enclosed quiet area of the Ontario Science Centre, while parents/guardians completed two questionnaires. One extensively trained examiner (K.W.)
conducted 53% of the interviews, while four other trained examiners conducted 24%, 13%, 7%, and 3% of the interviews respectively. Upon completion of the interview, participants received a certificate of participation and a pencil. All procedures were approved by the Human Participants Review (Ethics) Sub-Committee of York University and the Research Ethics Board of SickKids.

2.2.3 Demographic Information

Demographic information was obtained from parents/guardians who completed a detailed demographic questionnaire, which yielded information about the child’s age, sex, ethnicity, primary language, overall health, psychiatric health, the parents’ marital status, and family SES. Nine parents/guardians chose not to complete the demographic questionnaire but did indicate their child’s age and sex.

2.2.4 Children’s Autobiographical Interview

Participants’ AM performance was assessed using the Children’s Autobiographical Interview (CAI), which was developed for the present study and is an adapted version of Levine et al.’s (2002) Autobiographical Interview (see Appendix A for a comparison between the CAI and the Autobiographical Interview). For the CAI, participants were required to recall two AMs that occurred at a specific time and place more than one month previously (see Appendix B for instructions). In order to assist with memory retrieval, participants were shown a list of 18 sample autobiographical events (e.g., your last birthday), but were also told that they did not necessarily have to choose an event from that list (see Appendix C for the list of sample events). The CAI had three distinct phases: free recall, general probe, and specific probe. In the free recall phase, participants described as many details as they could remember about the event without interruption until either it became clear that the end of their description was reached or five minutes had elapsed. After the initial description of the event, general probes were given to encourage greater recall of details (e.g., “Is there anything else you can tell me about that
event?”) or to narrow down overly-general or multiple event descriptions into a single event (e.g., “You described a couple of events. I would like you to only tell me about one of those events. Choose the one that you feel you remember the best”). If participants were unable to produce a specific event after general probing, they were given the opportunity to choose a different event to describe. Finally, in the specific probe phase, participants answered a series of standardized questions that served to promote retrieval of any episodic details that were not recalled in the previous phases (e.g., “When did this event take place?”). In order to prevent the specific probe process from contaminating free recall of the second event, specific probing was administered after both events had been described under both free recall and general probe phases. After the specific probing phase, participants provided a self-report rating of how well they could visualize each event at the time of recollection using a 7-point scale (1 = can’t see it at all, 7 = really clear like I am seeing it in front of me).

2.2.4.1 Scoring Protocol for the Children’s Autobiographical Interview

Each participant’s tape-recorded interview was transcribed, double-checked for any transcription errors by K.W., and then subsequently scored according to the Autobiographical Interview Scoring Manual (Levine et al., 2002). The transcribed text was segmented into two main categories of details: episodic and non-episodic. Details were defined as episodic if they were directly related to the event described, were specific in time and place, and conveyed a sense of episodic re-experiencing. These details were then assigned to one of five episodic detail subcategories: (a) event, (b) place, (c) time, (d) perceptual, and (e) emotion/thought (see Appendix D for a scoring example). The remaining details were considered non-episodic and were assigned to one of four non-episodic detail subcategories: (a) semantic facts, (b) unsolicited repetitions of previously recalled details, (c) other metacognitive statements, and (d) external event details unrelated to the main event recalled (see Appendix D for examples). Details were
then tallied for each episodic and non-episodic subcategory, and summed to form total episodic and total non-episodic detail composite scores across each phase of the CAI (e.g., free recall, general probe, and specific probe). Each AM was also assigned qualitative experimenter ratings assessing episodic richness, time, place, perception, emotion/thought, and time integration (see Appendix E for a detailed description and example of each rating category). A total experimenter rating composite was created by summing the five ratings pertaining to episodic re-experiencing (e.g., episodic richness, time, place, perception, and emotion/thought) and had a scale from 0 to 18. The time integration rating, reflecting one’s ability to integrate the event into a larger time scale or life history was assessed separately and had a scale from 0 to 3. For each participant, the AM detail scores, experimenter ratings, and self-report visualization ratings were averaged across their two AMs. All memories were first scored by K.W. and then for reliability, re-scored by a second individual. Both scorers were blind to participants’ age and sex, and had undergone extensive training using a practice set of 20 AMs. Inter-rater reliability was assessed using intra-class correlation (one-way random effects model; McGraw & Wong, 1996). Coefficients for total episodic and total non-episodic details were 0.92 and 0.98 for free recall, 0.97 and 0.90 for general probe, and 0.96 and 0.89 for specific probe. Coefficients for the episodic subcategories ranged from 0.74 to 0.95, and coefficients for the non-episodic subcategories ranged from 0.78 to 0.83.

2.2.5 *Everyday Memory Questionnaire*

Parents/guardians completed the Everyday Memory Questionnaire (EMQ; Sunderland et al., 1983), which was comprised of 28 items assessing any difficulties in their child’s memory ability in everyday life situations along a 9-point scale ranging from 1 (*not at all in the last 3 months*) to 9 (*more than once a day*). Lower EMQ scores signified better everyday memory. Using a factor structure developed by Cornish (2000), three composite scores were created: (a) memory for
everyday activities (i.e., from 5 items, e.g., ‘forgets a change in his/her daily routine’), (b) spatial everyday memory (i.e., from 4 items, e.g., ‘gets lost where he/she has often been before’), and (c) a total EMQ composite based on the square root of the sum of all 28 items. Twenty-six parents/guardians chose not to complete the EMQ (note: missing data were equally distributed across age groups).

2.2.6 Data Analysis

Given that very few details from the CAI were recalled during the general probe phase, details from the first two phases (i.e., free recall and general probe) were collapsed to form a single ‘Recall’ condition. This Recall condition was analyzed separately from a ‘Recall + Specific Probe’ condition, which comprised participants’ cumulative scores across all three phases of the CAI. Similar to Levine et al. (2002), the specific probe phase was not examined in isolation because it would have penalized participants who provided richly detailed accounts in the free recall phase and consequently, received fewer probing questions in the specific probe phase. In addition, direct statistical comparisons between scores in the Recall condition and the Recall + Specific Probe condition could not be conducted because these scores were highly correlated. Therefore, in order to examine the effects of retrieval support, we assessed whether any significant effects found in the Recall condition were reduced to non-significant effects in the Recall + Specific Probing condition (i.e., following the addition of probing questions).

All variables of interest were first examined for outliers (i.e., > 3 SD from the mean) and any outliers found were replaced with the highest or lowest reasonable score using Winsorization (Field, 2009; Grace & Sawilowsky, 2009; Note: results were identical when outliers were not replaced). In addition, all variables were examined for deviations in skewness and kurtosis in order to assess the assumption of normality. A few AM variables that exceeded the cutoffs for skewness (± 2) and kurtosis (± 2) were corrected using log10 transformation (see Appendix F for
skewness and kurtosis values for these variables before and after transformation). In all analyses, exact chronological age (in days) was used and the overall significance level was set at $p < .01$ in order to control for large number of regression analyses conducted, which may increase the risk of making Type I errors. Given that the demographic variables (e.g., SES, ethnicity) and examiner (e.g., K.W., D.B., etc.) had no effect on the results when used as covariates in each of the regression analyses, these variables were not considered further.

In order to examine age-related differences in episodic and semantic AM, hierarchical linear regressions were used with sex and retention interval (i.e., delay since the event, measured in years) entered as control variables in step one, followed by age as the predictor variable in step two. Sex was used as a control variable because numerous studies have shown that females have better episodic AM than males across the lifespan because they recall more detailed, accurate, vivid, and emotional AMs than males (Buckner & Fivush, 1998; Davis, 1999; Pillemer, Wink, DiDonato, & Sanborn, 2003; Ross & Holmberg, 1992). In addition, retention interval (i.e., $M = 1.97$ years; $SD = 1.95$ years; averaged across the two AMs) was also used as a control variable because it was negatively correlated with the number of event details, $r = -.158$, $p = .033$, and time details, $r = -.166$, $p = .025$, recalled in the Recall + Specific Probe condition. Hierarchical linear regressions were also used to determine whether participants’ self-report visualization ratings predicted the number of episodic AM details recalled, with age, sex, and retention interval entered as control variables. Finally, to examine age-related differences in everyday memory, hierarchical linear regressions were used with sex as the control variable and age as the predictor variable. All variables were standardized before being entered in each regression analysis.

2.3 Results

2.3.1 Effect of Age on AM Performance in the Recall Condition
Figure 2.1a presents means and standard errors of total episodic and total non-episodic details in the Recall condition across age. As shown in Table 2.2a, age significantly predicted both total episodic and total non-episodic details in the Recall condition; however age accounted for a greater proportion of the variance for total episodic details, $\Delta R^2 = 0.17$, than for total non-episodic details, $\Delta R^2 = 0.07$ (note: a t-test revealed that the correlation coefficient between age and total episodic details, $r = .402$, was significantly greater than the correlation coefficient between age and total non-episodic details, $r = .268; t = 2.12, p < .05$). Generally, older participants recalled more episodic and non-episodic details than younger participants. In addition, age significantly predicted all five episodic subcategories (i.e., event, place, time, perceptual, and emotion/thought details) and three out of the four non-episodic subcategories (i.e., semantic details, repetitions, and other metacognitive statements), with older participants recalling more details than younger participants (see Table 2.2b & c). Importantly, age also accounted for a greater proportion of the variance for all episodic subcategories than for all non-episodic subcategories, including semantic details (see Table 2.2b & c for $\Delta R^2$ values).

2.3.2 Effect of Age on AM Performance in the Recall + Specific Probe Condition

Next, the effect of age on total episodic and total non-episodic details was examined for the Recall + Specific Probe condition, after the provision of retrieval support (i.e., specific probing). As shown in Table 2.3 and Figure 2.1b, age significantly predicted total episodic and total non-episodic details, all five episodic subcategories, and three out of the four non-episodic details (i.e., semantic details, repetitions, and other metacognitive statements). In each case, older participants recalled more details than younger participants. Again, age accounted for a greater proportion of the variance for the episodic detail composite and subcategories scores than for the non-episodic detail composite and subcategories scores (see Table 2.3 for $\Delta R^2$ values). In addition, a t-test revealed that the correlation coefficient between age and total episodic details in
the Recall + Specific Probe condition, \( r = .368 \), was significantly greater than the correlation coefficient between age and total non-episodic details, \( r = .238; t = 2.07, p < .05 \).

Given that the experimenter ratings provided a secondary measure of the overall quality of participants’ AMs that corresponded to Piolino et al.’s (2007) measure of episodic AM, we examined whether age predicted the experimenter rating composite and/or the time integration rating. As shown in Table 2.3d, age significantly predicted both the experimenter rating composite and time integration rating. In each case, older participants received higher ratings of the overall quality of their AM recollections and their ability to integrate each AM into a larger time scale or life history than younger participants.

2.3.3 Effect of Participants’ Visualization Ratings on Episodic AM Performance
Hierarchical linear regressions were used to examine whether participants’ self-report ratings of their ability to visualize each AM at the time of recollection predicted episodic AM performance in Recall + Specific Probe condition. Results indicated that higher visualization ratings significantly predicted a greater number of total episodic details recalled, \( \Delta F(1,177) = 9.74, \Delta R^2 = 0.04, B = 0.198, p = .002 \). In addition, higher visualization ratings also significantly predicted a greater number of perceptual details, \( \Delta F(1,177) = 12.96, \Delta R^2 = 0.06, B = 0.246, p < .001 \), time details, \( \Delta F(1,177) = 10.87, \Delta R^2 = 0.05, B = 0.219, p = .001 \), and emotion/thought details, \( \Delta F(1,177) = 6.83, \Delta R^2 = 0.03, B = 0.160, p = .010 \), recalled.

2.3.4 Effect of Age on Everyday Memory and its Relation to Episodic AM
Finally, the effect of age on everyday memory performance was also examined using hierarchical linear regressions in order to determine whether similar age-related differences would be found in everyday memory as those observed in episodic AM recall. Results indicated that age significantly predicted the EMQ composite, \( \Delta F(1,151) = 6.64, \Delta R^2 = 0.04, B = -0.20, p = .011 \), and the subscales representing spatial everyday memory, \( \Delta F(1,153) = 10.25, \Delta R^2 = \).
0.06, $B = -0.24$, $p = .002$, and memory for everyday activities, $\Delta F(1,155) = 7.21$, $\Delta R^2 = 0.04$, $B = -0.21$, $p = .008$. In each case, older participants had lower EMQ scores, signifying better everyday memory ability, than younger participants (see Table 2.4 for means and standard deviations across age). In order to determine whether age-related increases in everyday memory corresponded with those found in episodic AM, the EMQ data were re-analyzed after first controlling for episodic AM (i.e., total episodic details in the Recall + Specific Probe condition). Results from these analyses indicated that the effects of age on everyday memory were significantly reduced for the EMQ composite ($p = .018$) and memory for everyday activities subscale ($p = .027$), but not for the spatial everyday memory subscale ($p = .005$), after controlling for episodic AM.

### 2.4 Discussion

This study examined age-related differences in episodic and semantic AM, as well as everyday memory, in a large sample of typically developing children and adolescents between 8 to 16 years of age. More specifically, the newly developed Children’s Autobiographical Interview was used to determine whether the number of episodic and semantic AM details recalled within a single autobiographical narrative increased across both childhood and adolescence. The results were consistent with Piolino et al.’s (2007) and Picard et al.’s (2009) findings of gradual age-related increases in episodic AM across childhood. However, our results also indicated that these improvements extend well into adolescence. In addition, the present study also demonstrated robust age-related improvements within each subcategory of episodic AM details (i.e., event, time, place, perceptual, and emotion/thought), indicating that the overall quality of children’s episodic AM significantly improves across childhood and adolescence. Similar to Picard et al.’s (2009) results, we also found significant improvements in semantic AM across childhood and adolescence. Importantly, age accounted for a greater proportion of the variance in the number of
total episodic details recalled than in the number of semantic details (or total non-episodic
details) recalled across both Recall and Recall + Specific Probe conditions. Thus, our results
indicate that both episodic and semantic AM improved significantly with age; however, greater
age-related differences were evident in episodic AM than semantic AM.

Several researchers have suggested that improvements in episodic AM across childhood
and adolescence may be particularly associated with prolonged maturation of the prefrontal
cortex and its memory retrieval and executive processes (e.g., Levine, 2004; Piolino et al., 2007).
In the present study, age effects were similar across the Recall and Recall + Specific Probe
conditions, indicating that high retrieval support did not significantly reduce the age effect. Thus,
age-related differences in episodic AM during childhood and adolescence may not be solely due to
improvements in uncued retrieval and memory search operations associated with the prefrontal
cortex but may also depend on maturation of the hippocampus and the entire AM neural network, as
well as other cognitive functions. For example, Picard et al. (2009) showed that episodic AM
development is not only associated with improved executive functioning, which relies on the
prefrontal cortex, but also with improved verbal episodic memory, which largely relies on the
hippocampus. In addition, increases in both gray matter volume and synaptic connectivity within
the hippocampus have been observed across childhood and adolescence (Benes et al., 1994;
Grieve et al., 2011; Huttenlocher & Dabholkar, 1997) and could contribute to age-related
improvements in episodic AM. Given that AM relies on several diverse cognitive processes, as
well as an entire network of brain regions (Svoboda et al., 2006), it is likely that numerous
factors account for age-related differences in episodic AM during childhood and adolescence.
Thus, additional investigations using both behavioural and neuroimaging techniques are required
to investigate structure-function relations associated with episodic and semantic AM during
childhood and adolescence.
Participants’ self-report ratings of their ability to visualize past events at the time of recollection were also examined in order to determine whether greater visualization during retrieval is associated with better AM performance. The results indicated that higher visualization ratings were associated with a greater number of episodic AM details recalled, particularly within the perceptual subcategory. This finding supports the idea that visual imagery is an important feature of episodic AM retrieval (Addis et al., 2004; Rubin & Greenberg, 1998). Interestingly, previous neuroimaging studies have shown that vividly re-experienced AMs are associated with increased hippocampal activation (e.g., Addis et al., 2004; Gilboa et al., 2004), suggesting a specific role for the hippocampus in re-experiencing and visualizing past events.

Given that normal hippocampal functioning is essential for both episodic AM and everyday memory (Isaacs et al., 2000; Vargha-Khadem et al., 1997), age-related differences in everyday memory were examined to determine whether these differences were similar to those observed in episodic AM. The results indicated that age significantly predicted everyday memory ability, specifically memory for everyday activities and spatial everyday memory. In addition, the effect of age on memory for everyday activities was significantly reduced after first controlling for episodic AM. This finding suggests that age-related increases in everyday memory, particularly memory for everyday activities, correspond with age-related increases in episodic AM, possibly because these abilities are dependent on the maturation of similar brain regions (e.g., the hippocampus) or neural networks. However, further investigation of the relation between episodic AM and everyday memory using longitudinal data and neuroimaging techniques is required.

Two important limitations of the present study warrant discussion. First, we were not able to verify the details of participants’ AMs to determine if they accurately represented the original event details. It is often difficult to assess the accuracy of children’s AMs without creating a staged autobiographical event, given that parental verification of event details can also be
inaccurate or biased and parents are unable to verify details from events in which they were not present (e.g., sleepovers or school trips). However, because our sample size was relatively large and our results replicated previous findings, we believe that our results accurately represent age-related differences in the ability to recall episodic and semantic AM details. However, further investigations of AM using a staged event would be beneficial in order to examine the accuracy of children’s AMs. Second, due to the cross-sectional design of the present study, we were unable to identify individual developmental trends in episodic and semantic AM. Therefore, our conclusions concerning age-related differences in episodic and semantic AM, as well as everyday memory, should be interpreted with this in mind. Clearly, longitudinal studies of episodic and semantic AM are required to further investigate these developmental trajectories.

In summary, the present study provides a detailed account of age-related differences in episodic and semantic AM across childhood and adolescence using the newly developed Children’s Autobiographical Interview. Although a considerable amount of research on AM has been conducted, most studies have not investigated both episodic and semantic AM together, especially during late childhood and adolescence. Thus, the present study provides important new insight into episodic and semantic AM, as well as the relation between episodic AM and everyday memory, during this often neglected developmental time period. However, in order to improve our understanding of the underlying neural mechanisms that support episodic and semantic AM retrieval and how they develop during childhood, further research using neuroimaging techniques is required. In addition, investigations into episodic and semantic AM in atypically developing children, such as children with early hippocampal damage, would be particularly useful for determining how abnormal brain development affects episodic and semantic AM performance.
Table 2.1

*Number of Males and Females at Each Age Group*

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Table 2.2

*Regressions with Age Predicting Episodic and Non-episodic Details in the Recall Condition after Controlling for Retention Interval and Sex*

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Note: B = unstandardized regression coefficient; * = p < .05, ** = p < .01, *** = p < .001
Table 2.3

Regressions with Age Predicting Episodic and Non-episodic Details in the Recall + Specific Probe Condition after Controlling for Retention Interval and Sex

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<td>0.07</td>
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<td>0.23**</td>
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<tr>
<td><strong>Other Statements</strong></td>
<td>1.38</td>
<td>0.02</td>
<td>0.10</td>
<td>11.15***</td>
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<td>0.22**</td>
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<td><strong>Non-episodic Event</strong></td>
<td>0.26</td>
<td>0.00</td>
<td>-0.03</td>
<td>0.58</td>
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<td>0.12</td>
<td>22.20***</td>
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<td>0.34**</td>
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<td><strong>Time Integration</strong></td>
<td>1.14</td>
<td>0.01</td>
<td>-0.01</td>
<td>35.09***</td>
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<td>0.07</td>
<td>0.16</td>
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<td>-0.11</td>
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<td>0.11</td>
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<td></td>
<td></td>
<td>0.42</td>
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</table>

Note: $B =$ unstandardized regression coefficient; * = $p < .05$, ** = $p < .01$, *** = $p < .001$
Table 2.4

*Means and Standard Deviations (in Parentheses) of the EMQ Composite and Two Subscales Across Age*

<table>
<thead>
<tr>
<th>Age</th>
<th>Number of Participants</th>
<th>EMQ Composite</th>
<th>EMQ Spatial</th>
<th>EMQ Memory for Activities</th>
</tr>
</thead>
<tbody>
<tr>
<td>8</td>
<td>N = 17</td>
<td>8.13 (2.12)</td>
<td>2.64 (1.58)</td>
<td>3.43 (1.91)</td>
</tr>
<tr>
<td>9</td>
<td>N = 16</td>
<td>8.32 (1.53)</td>
<td>2.11 (1.03)</td>
<td>3.47 (1.27)</td>
</tr>
<tr>
<td>10</td>
<td>N = 16</td>
<td>7.24 (1.26)</td>
<td>1.61 (0.63)</td>
<td>2.63 (1.24)</td>
</tr>
<tr>
<td>11</td>
<td>N = 21</td>
<td>7.36 (1.46)</td>
<td>1.95 (1.10)</td>
<td>2.72 (1.43)</td>
</tr>
<tr>
<td>12</td>
<td>N = 19</td>
<td>7.94 (1.67)</td>
<td>2.04 (0.93)</td>
<td>2.97 (1.43)</td>
</tr>
<tr>
<td>13</td>
<td>N = 18</td>
<td>7.51 (1.13)</td>
<td>1.43 (0.47)</td>
<td>3.18 (1.12)</td>
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<tr>
<td>14</td>
<td>N = 14</td>
<td>7.13 (1.18)</td>
<td>1.95 (0.90)</td>
<td>2.80 (1.14)</td>
</tr>
<tr>
<td>15</td>
<td>N = 18</td>
<td>6.99 (1.55)</td>
<td>1.72 (1.01)</td>
<td>2.39 (1.36)</td>
</tr>
<tr>
<td>16</td>
<td>N = 15</td>
<td>6.98 (1.22)</td>
<td>1.38 (0.42)</td>
<td>2.33 (1.04)</td>
</tr>
</tbody>
</table>

EMQ = Everyday Memory Questionnaire; Note: The EMQ composite is the square root of all 28 items and higher scores on the EMQ indicate poorer everyday memory ability.
Figure 2.1

*Mean Number of Total Episodic and Total Non-Episodic Details Recalled at Each Age Across the Two Conditions: Recall (a) and Recall + Specific Probe (b)*

(a) **Recall Condition**

- Total episodic details
- Total non-episodic details

(b) **Recall + Specific Probe Condition**

- Total episodic details
- Total non-episodic details

Error bars indicate standard error of the mean
Chapter 3
Study II: Effects of Early Thyroid Hormone Deficiency on Children’s Episodic and Semantic Autobiographical Memory Performance and HippocampalVolumes

3.1 Introduction

The hippocampus is a crucial brain structure for episodic autobiographical memory (AM) because it binds and integrates contextual details present at the time of encoding and is involved in retrieving and perceptually re-experiencing past events (Eichenbaum & Bunsey, 1995; Gilboa et al., 2004; Moscovitch, 2008). The hippocampus also requires an adequate supply of thyroid hormone (TH) for proper development and therefore, is susceptible to damage following periods of early TH deficiency (Bernal & Nunez, 1995). In humans, two conditions of early TH deficiency that differ in their specific timing of TH loss are maternal hypothyroidism during pregnancy (HYPO) and congenital hypothyroidism (CH). In HYPO, the fetus is exposed to insufficient maternal TH levels throughout gestation, with more severe TH deficiency occurring within the first half of gestation when the developing fetal thyroid is not yet functional (see Figure 1.2a; Zoeller & Rovet, 2004). In contrast, individuals with congenital hypothyroidism (CH) receive an adequate supply of maternal TH during gestation but are unable to produce sufficient levels of their own TH during late gestation and after birth due to fetal thyroid gland dysfunction (Zoeller & Rovet, 2004).

Animal models of CH and HYPO conditions have shown that the timing of early TH deficiency has important consequences for the type of structural impairments that can result within the hippocampus. For example, early prenatal TH deficiency (or HYPO) appears to have a more significant impact on overall hippocampal structure (e.g., volume) because it impairs neurogenesis and neuronal migration within a much larger region of the developing hippocampus (i.e., the CA1 field) than postnatal TH deficiency, which tends to impair the small and late-
developing dentate gyrus (Ausó et al., 2004; Gilbert & Paczowski, 2003; Hasegawa et al., 2010; Lavado-Autric et al., 2003). However, both prenatal and postnatal TH deficiency have been associated with abnormal synaptic function within hippocampal neural circuits and these abnormalities have been associated with functional impairments in learning and memory in rats (Liu et al., 2010; Reid et al., 2007). Recent studies of children with early-treated CH indicate that this population exhibits weaknesses in verbal episodic memory (i.e., story recall) and delayed visuospatial memory (Oerbeck et al., 2005; Rovet, 1999), as well as reduced left hippocampal volumes relative to controls (Wheeler et al., 2011). Although children born to treated hypothyroid women exhibit similar visuospatial impairments as children with early-treated CH, no study has yet examined verbal episodic memory performance or hippocampal volumes in this population (Man et al., 1992; Mirabella et al., 2005). In addition, no study has specifically examined episodic AM and its relation to hippocampal volume in either CH or HYPO groups.

Thus, the main aim of the present study was to use the Children’s Autobiographical Interview (CAI) to investigate the effects of early TH deficiency on episodic and semantic AM performance during childhood. Numerous studies have used Levine et al.’s (2002) Autobiographical Interview, from which the CAI was developed, to demonstrate that adult patients with hippocampal damage exhibit impairments in episodic AM, but not semantic AM (Addis et al., 2007; Rosenbaum et al., 2008; 2011; Steinworth et al., 2005; St-Laurent et al., 2009). In addition, St-Laurent et al. (2009) used the Autobiographical Interview to show that patients with hippocampal damage are particularly impaired in recalling perceptual (e.g., visual) details from past autobiographical events. This finding corresponds with evidence indicating that the hippocampus plays an important role in visual imagery and rich perceptual re-experiencing of past events (Gilboa et al., 2004; Rubin & Greenberg, 1998). Importantly, no study has yet used to the CAI to examine episodic and semantic AM in children with abnormal hippocampal
development. Based on St-Laurent et al.’s (2009) findings, and the fact that CH and HYPO conditions are both associated with weak visual abilities (Mirabella et al., 2005), it was expected that both CH and HYPO groups would recall fewer episodic AM details, particularly within the visual-perceptual subcategory, but not fewer semantic AM details, than controls.

A second goal of the present study was to compare hippocampal volumes in CH and HYPO groups and typically developing controls using structural MRI (see section 3.2.8 for a detailed description of structural MRI). Based on animal research suggesting that early prenatal TH deficiency may be associated with more severe structural damage to the hippocampus than postnatal TH deficiency (Ausó et al., 2004; Hasegawa et al., 2010; Lavado-Autric et al., 2003; Madeira et al., 1992), it was expected that relative to typically developing controls, the HYPO group would exhibit greater reductions in hippocampal volume than the CH group. Unfortunately, it was not possible to distinguish specific subregions of the hippocampus that are differentially affected by the timing of early TH deficiency (i.e., the CA1 field and dentate gyrus) due to the low resolution of structural MRI scans collected from a 1.5T scanner (i.e., the only scanner available at the start of this study). As a proxy, however, we examined anterior and posterior subregions of the hippocampus, which are thought to be involved in different memory functions (e.g., anterior for encoding and posterior for retrieval; Kircher et al., 2008; Le Page, Habib, & Tulving, 1998; Strange, Fletcher, Henson, Friston, & Dolan, 1999). Given that early TH deficiency has been shown to specifically impair the CA1 field (Ausó et al., 2004; Berbel et al., 2010) and dentate gyrus (Gilbert & Paczowski, 2003; Gilbert & Sui, 2005), which both extend through both anterior and posterior sections of the hippocampus, we expected that that children with early TH deficiency would exhibit structural abnormalities within both the anterior and posterior regions of the hippocampus.
Structure-function relations between hippocampal volumes and episodic AM recall performance were also examined in both TH-deficient and control groups. Several studies have previously found that reductions in hippocampal volume are associated with poorer episodic AM performance in patients with temporal lobe epilepsy (Noulhiane et al., 2007) and patients with Alzheimer’s disease (Gilboa et al., 2005). Based on these findings, smaller hippocampal volumes in either CH or HYPO groups were expected to predict poorer episodic AM performance. Finally, in order to investigate whether children who experienced more severe TH deficiency exhibited smaller hippocampal volumes and poorer memory performance than those who experienced less severe TH deficiency, we examined whether elevated thyroid stimulating hormone (TSH) values, during gestation for HYPO (i.e., maternal TSH values) and at birth or at diagnosis for CH, predicted these variables. TSH values were used as a marker of the severity of early TH deficiency because they are thought to be the most sensitive and reliable measure of thyroid function abnormalities (Glinoer & Spencer, 2010) and the TSH test was the most consistently used test across both CH and HYPO groups.

3.2 Methods

3.2.1 Participants

Eight-five children (47% male) between the ages of 9 and 14 years ($M = 10.44; SD = 1.10$) were recruited for the present study. This sample included 26 children with CH, 27 HYPO, and 32 typically developing controls. The 26 CH participants were recruited from either a list of past or current participants within our lab ($N = 17$; of which 15 were from a longitudinal cohort recruited at birth) or the Endocrine Clinic at SickKids ($N = 9$). All CH participants except one were identified at birth through the Ontario newborn screening program, which uses a thyroid stimulating hormone (TSH) test to screen for hypothyroidism (see Table 3.1 for newborn TSH values in CH). The exception was a male born outside of Canada and diagnosed at 15 days of
The CH group consisted of nine children with athyrosis (i.e., an absent or dysfunctional thyroid gland), 14 with ectopic or lingual glands (i.e., an abnormally located thyroid gland), one with dyshormonogenes (i.e., a defect in TH synthesis), and two with unknown etiologies. The HYPO group was entirely recruited from a list of past participants who belonged to a cohort recruited at birth and were followed throughout childhood at SickKids. Mothers of the HYPO group were originally identified through the SickKids’ Motherisk program or through local endocrinologists (see Table 3.1 for maternal TSH values during pregnancy). Finally, all controls were recruited from a list of past or current participants, 28 of whom were from the longitudinal cohort.

Exclusionary criteria for all participants were exposure to alcohol or other teratogens during pregnancy, a head injury or neurological disease, neuroradiological abnormalities, a debilitating or chronic medical condition, an IQ score below 80, and a psychiatric diagnosis. Additional exclusionary criteria for controls were an identified learning disability and a diagnosis of ADHD. Two controls were excluded from the analyses, one with a learning disability and with ADHD. In addition, four HYPO participants were excluded from the analyses, one with a neuroradiological abnormality (i.e., a frontal dysembryoplastic neuroepithelial tumor) and three because their mothers’ TSH values were within a normal range throughout pregnancy. Thus, the remaining sample of participants included 79 children (47% male) between the ages of 9 and 14 years (M = 10.48, SD = 1.12) and was comprised of 26 CH, 23 HYPO, and 30 controls. Within this sample, seven participants did not complete the structural imaging portion of the study because they were wearing braces (2 CH), did not want to undergo scanning (1 CH, 3 HYPO), or moved so excessively during the scan that their data had to be discarded (1 CH). All participants were fluent or native English speakers. Family Hollingshead SES scores (Hollingshead, 1975) ranged from 26 to 76 (M = 50.02, SD = 10.00), including 4% in the medium-low income range.
12% in the medium income range, 51% in the medium-high income range, and 33% in the high income range.

3.2.2 General Procedure

All parents provided written consent for participation in this study while participants also provided verbal assent. Participants were individually tested in the Psychology Department at SickKids over the course of two days, which were separated by a period of approximately four and a half months ($M = 4.74; SD = 2.55$). On Day 1, participants took part in a clinical neuropsychological assessment that examined intelligence and multiple aspects of memory, while parents completed several questionnaires. Eighty-one percent of participants also took part in a staged autobiographical event that was assessed in Study III. At the end of Day 1, participants received a certificate of participation, a movie gift certificate, and parents were compensated for transportation.

On Day 2, participants were interviewed using the Children’s Autobiographical Interview (CAI). One examiner (K.W.) conducted 99% of the interviews, while a second trained examiner conducted one interview for a CH participant. Immediately after the CAI, participants underwent structural MRI scanning in a 1.5 Tesla Signa GE scanner, during which they viewed movies via MRI-compatible goggles in the Diagnostic Imaging Unit at SickKids. A neuroradiologist examined all MRI images for neuroradiological abnormalities and sent written reports to participants’ family physicians. Upon completion of Day 2, participants received a movie gift certificate and a CD containing several pictures of their own brain. Parents received compensation for transportation and a clinical report describing their child’s performance on the neuropsychological assessment from Day 1. All procedures were approved by the Research Ethics Board of SickKids and the Office of Research Ethics at the University of Toronto.

3.2.3 Demographic Information
Demographical information was obtained from all parents using the same demographic questionnaire from Study I.

3.2.4 Early TSH Levels and TH Treatment Values for CH and HYPO

For CH participants, information on early TSH and TH treatment values were obtained from medical health records at SickKids (see Table 3.1 for missing cases). For HYPO participants, maternal TSH and TH treatment values during pregnancy were obtained from the participants’ family physicians (see Table 3.1 for missing cases).

3.2.5 Clinical Neuropsychological Assessment of Intelligence and Memory

During the clinical neuropsychological assessment on Day 1, participants were assessed for intelligence, verbal episodic memory, general semantic memory, and delayed visuospatial memory. Intelligence was assessed using the Vocabulary and Matrix Reasoning subtests of the Wechsler Abbreviated Scale of Intelligence (WASI; Wechsler, 1999), which yields an estimate of Full Scale IQ. Verbal episodic memory was examined using the Stories subtest of the Children’s Memory Scale (CMS; Cohen, 1997), which required participants to listen to two stories and after each, recall the story verbatim immediately and after a 30-minute delay. Only delayed recall scores, reflecting the average number of correctly recalled details from the two stories after the delay, were used in the present study. This subtest was chosen because previous studies have shown that children with early TH deficiency exhibit difficulties in recalling story details (Oerbeck et al., 2005; Wheeler et al., 2011).

General semantic memory was assessed using the Information subtest of the Wechsler Intelligence Scale for Children 4th Edition (WISC-IV; Wechsler, 2003), which contained 25 questions assessing participants’ general knowledge about common events, objects, places, and people (e.g., What must you do to make water boil?, Who was Christopher Columbus?, etc.). The
WISC Information score reflected the total number of correct responses. This subtest was chosen because the adult version of this subtest has been used previously to examine general semantic memory performance in adult patients with hippocampal damage (Noulhiane et al., 2007; Rosenbaum et al., 2011; Steinworth et al., 2005; Zola-Morgan et al., 1986). Both the CMS and WISC scores were converted into scaled scores based on age norms for group comparisons.

Delayed visuospatial memory was assessed using the Rey-Osterrieth Complex Figure task (Rey-O; Osterrieth & Rey, 1944; Rey, 1942), which required participants to first copy a complex figure shown on a stimulus card and then recreate it from memory after a 30-minute delay. For each condition, drawing accuracy was scored using a comprehensive 36-point scale (Spreen & Strauss, 1998) and only the delayed recall condition was analyzed presently. This task was chosen because it has been used extensively to investigate memory impairments in adults with hippocampal damage (Addis et al., 2007; Steinworth et al., 2005; Zola-Morgan et al., 1986), children with early TH deficiency (Oerbeck et al., 2005; Wheeler et al., 2011), children with temporal lobe epilepsy (Jambaqué et al., 2007; Mabbot & Smith, 2003), and individuals with developmental amnesia (Rosenbaum et al., 2011; Vargha-Khadem et al., 1997; 2003). Three CH participants did not complete the CMS and Rey-O, and seven controls and 14 CH did not complete the Information subtest of the WISC because they were recruited from two separate ongoing studies within our lab that involved alternate batteries of clinical tests.

3.2.6 Everyday Memory Questionnaire

Parents completed the same 28-item Everyday Memory Questionnaire (EMQ; Sunderland et al., 1983) from Study I. Only the total EMQ composite score (i.e., the square root of the sum of all 28 items) was analyzed in the present study. Lower EMQ scores signified better everyday memory. Three parents from the CH group did not complete the EMQ because they were recruited from a separate ongoing study within our lab that did not include this questionnaire.
3.2.7 Children’s Autobiographical Interview

AM was assessed using the same Children’s Autobiographical Interview (CAI) from Study I (see Study I for a more detailed description of the CAI). For the present study, however, participants were: (a) instructed to recall two specific AMs that had occurred within the last three years but not within the past month, in order to create a more restricted time period; and (b) told to choose events only from the provided list of sample AMs (see Appendix C) in order to reduce variability of event type across participants (Note: 81% of participants were also asked to recall a staged autobiographical event experienced on Day 1 for the purposes of Study III and 52% of participants were also asked to recall two additional naturally occurring AMs for the purposes of Study IV, after first recalling the two AMs assessed in the present study). Similar to Study I, participants completed all three phases of the CAI (i.e., free recall, general probe, and specific probe) for each AM and provided self-report ratings of their ability to visualize each AM at the time of recollection.

3.2.7.1 Scoring Protocol for the Children’s Autobiographical Interview

The CAI scoring protocol was identical to Study I, except that the perceptual detail subcategory was further subdivided into visual and non-visual detail categories. Visual details included colours, objects that were part of the perceptual landscape and not directly involved in the event (e.g., ‘there were lots of trees’), and object characteristics (e.g., ‘it was round’). In contrast, non-visual details included sounds, smells, tastes, tactile feelings (e.g., ‘it was soft’), physical sensations (e.g., ‘I was tired’), body positions, one’s orientation in space, the location of other objects or people, and the duration of the event. All memories were first scored by K.W. and then for reliability, 38% of the AMs selected at random within each group (i.e., 10 CH, 10 HYPO, 10 CON) were re-scored by a second trained individual. Both scorers were blind to participants’ group, age, and sex. Inter-rater reliability was assessed using intra-class correlations.
and coefficients for total episodic and total non-episodic details were 0.99 and 0.80 for free recall, 0.97 and 0.97 for general probe, and 0.91 and 0.72 for specific probe. Coefficients for the episodic subcategories ranged from 0.71 to 0.95 and for the non-episodic subcategories, from 0.70 to 0.84.

3.2.8 Structural MRI Acquisition, Processing, and Hippocampal Volumes

Structural images used for volumetric analysis were collected using a 3D FSPGR (IR prep Zip X2) T1-weighted series in the axial plane (TR = 10.37ms, TE = 4.26ms, TI = 400ms, flip angle = 20°, field of view = 240mm, slice thickness = 1.50mm, no gap). During structural MRI, short radio frequency electromagnetic wave pulses are applied to the brain, causing changes to the orientation and energy state of hydrogen nuclei dipoles that normally align parallel to the scanner’s magnetic field (Amaro & Barker, 2006). After the radio frequency pulse is applied, hydrogen nuclei dipoles release photon energy as they slowly return to their equilibrium low-energy state, however, the rate of ‘relaxation’ differs depending on the properties of nearby tissue (Amaro & Barker, 2006). Thus, a structural T1 image can be constructed by measuring the signal associated with different relaxation times of hydrogen nuclei dipoles in different tissues, allowing one to differentiate between gray matter, white matter, and cerebral spinal fluid (Amaro & Barker, 2006). Post-processing of MRI images involved extracting brain images from the skull and cerebral spinal fluid and normalizing to standard space using anterior and posterior commissure alignment. Intracranial volumes were determined using SPM5 software (Statistical Parametric Mapping 5; Wellcome Department of Imaging Neuroscience). One trained analyst (K.W.), masked to group status, manually traced both left and right hippocampal volumes on a slice-by-slice basis with a trackball-driven cursor using ANALYZE 9.0 software (see Figure 3.1 for an illustration of this technique). Manual tracing was used in the present study because evidence has indicated that manual tracing is more precise in delineating the hippocampus from
surrounding structures and accounting for individual variation in hippocampal shape and size than automated volumetric methods (e.g., FreeSurfer; Lenroot & Giedd, 2006; Tae, Kim, Lee, Nam, & Kim, 2008).

Designation of the hippocampal region included the CA fields, dentate gyrus, and the subiculum. Hippocampal boundaries were outlined from anterior to posterior in coronal images, such that designation began at the rostral end when the hippocampal head first appeared below the amygdala and ended when the crura of the fornices departed from the hippocampal tail at the caudal end (Pruessner et al., 2000). In addition, each hippocampus was subdivided into anterior (i.e., hippocampal head) and posterior (i.e., hippocampal body and tail) segments along the coronal axis using the uncus as an unambiguous dividing marker (see Figure 3.1), following procedures outlined in Weiss, DeWitt, Goff, Ditman, and Heckers (2005). To reduce manual tracing errors, coronal images were magnified three times and both sagittal and transverse images were also used to verify hippocampal boundaries. A second extensively trained image analyst traced 34% of right and left hippocampal volumes, selected at random within each group (9 CH, 9 HYPO, 9 CON). Inter-rater reliability was assessed using intra-class correlations (one-way random effects model; McGraw & Wong, 1996) and coefficients were 0.77 (Cronbach $\alpha = 0.90$) for the right hippocampus and 0.84 (Cronbach $\alpha = 0.94$) for the left hippocampus.

### 3.2.9 Data Analysis

Similar to Study I, details from the first two phases of the CAI (i.e., free recall and general probe) were collapsed to form a single ‘Recall’ condition that was analyzed separately from the cumulative ‘Recall + Specific Probe’ condition. All variables of interest were first examined for outliers (i.e., $> 3$ SD from the mean). No outliers were found in hippocampal volumes, clinical memory scores, or early TSH values. However, outliers were found in the AM data and these were replaced with the highest or lowest reasonable score from that particular group (e.g., CH,
HYPO, or CON) using Winsorization (Field, 2009; Grace & Sawilowsky, 2009; Note: results were identical when outliers were not replaced). All variables were also examined for deviations in skewness and kurtosis in order to assess the assumption of normality. The few variables that exceeded the cutoffs for skewness (±2) and kurtosis (±2) were corrected using log10 transformation (see Appendix G for skewness and kurtosis values of variables that exceeded the cutoffs). Only one variable, external event details (i.e., one of the non-episodic detail subcategories) from the Recall condition still exceeded the cutoff for skewness and kurtosis after transformation. Because most participants recalled very few external event details in the Recall condition (see Figure 3.5a; \( M = 0.23, SD = 0.60 \)), this variable was excluded. A few AM variables were also significantly non-normal using the Kolmogorov-Smirnov test. However, parametric tests were used in the present study because: (a) the results were identical to those produced using non-parametric tests (see Appendix H for the results using non-parametric Mann-Whitney Tests), (b) our sample sizes were relatively large for the AM analyses (e.g., \( N = 49 \) for the TH-deficient group and \( N= 30 \) for the control group), which reduces the need for non-parametric tests (Jekel, Katz, & Elmore, 2001); and (c) it was deemed important to use ANCOVA, which reduced bias by controlling for important covariates (e.g., age, sex, and retention interval) and provided effect sizes for group comparisons.

Chi-squared tests were used to compare group differences in sex distribution. Group differences in demographic measures, such as age (measured in years) and SES were examined using univariate analyses of variance (ANOVAs) and clinical neuropsychological measures were examined using univariate analyses of covariance (ANCOVAs), after controlling for age and sex. For analyses of AM, group differences in total internal and total external details were studied using a mixed-factor ANCOVA, with detail category (episodic/non-episodic) as the repeated measure and group as the between-subjects variable, controlling for age, sex, and retention
interval. Retention interval \((M = 1.12 \text{ years}; SD = 0.73 \text{ years};\) averaged across the two AMs) was used as a covariate for consistency across studies; however, retention interval did not differ across groups \((p = .338;\) see Table 3.2 for group means and standard deviations) and was not significantly correlated with any of the AM variables in the present study. Group differences in the episodic and non-episodic detail subcategories were examined using two separate mixed-factor ANCOVAs (i.e., applying the Greenhouse-Geisser correction), with the specific detail subcategories (e.g., event, place, time, perceptual, and emotion/thought; or semantic details, repetitions, and other statements) as the repeated measure. Group differences in total visual and total non-visual episodic details, participants’ visualization ratings, and the experimenter ratings (i.e., total composite and time integration) were explored using ANCOVAs, controlling for age, sex, and retention interval. Hierarchical linear regressions were used to determine whether participants’ visualization ratings predicted total episodic details and visual details. For these analyses, age, sex, and retention interval were entered as covariates in step 1, dummy-coded group and visualization ratings were entered as predictors in step 2, and dummy-coded group-by-visualization rating interaction variables were entered in step 3.

Regarding the neuroimaging data, group differences in intracranial volumes were examined using ANCOVA, controlling for age and sex. Group differences in hippocampal volumes were examined using a mixed-factor ANCOVA, with hippocampal subregion (i.e., right posterior, right anterior, left posterior, and left anterior volumes) as the repeated measure and group as the between-subjects variable, controlling for age, sex, and intracranial volume. Intracranial volume was used as a covariate instead of creating ratio measures (i.e., dividing hippocampal volumes by intracranial volume) because Van Petten (2004) has argued that this method is more accurate in eliminating the average influence of total brain size on a particular brain structure. In order to investigate whether total hippocampal volumes predicted the total
number of episodic details recalled, a hierarchical linear regression was used with age, sex, retention interval, and intracranial volume entered as control variables in step 1, dummy-coded group variables and total hippocampal volumes entered as predictors in step 2, and the dummy-coded group-by-total hippocampal volume interaction variables entered in step 3.

Finally, hierarchical linear regressions were used to determine whether the severity of TH deficiency (i.e., elevated maternal TSH values during pregnancy for HYPO and elevated TSH values at birth and at diagnosis for CH) significantly predicted the following dependent variables: (a) total hippocampal volumes and individual hippocampal subregions, after controlling for age, sex, and intracranial volume; (b) total episodic details recalled, after controlling for age, sex, and retention interval; and (c) clinical memory scores (i.e., verbal episodic memory, general semantic memory, and delayed visuospatial memory), after controlling for age and sex. Given the exploratory nature of the present study in investigating the effects of early treated TH deficiency on memory ability and hippocampal volumes, an overall significance level of $p < .05$ was used and a few important trend-level effects (at $p < .10$) are discussed. However, effect sizes are reported and most results approached a significance level of $p < .01$.

3.3 Results

3.3.1 Early TSH Levels and TH Treatment Values for CH and HYPO

Early TSH levels and TH treatment values for CH participants and mothers of HYPO participants are shown in Table 3.1. All CH participants had elevated TSH values at birth and at diagnosis, indicating a late prenatal and early postnatal period of TH deficiency. In order to examine whether CH participants were adequately treated throughout infancy and childhood, an ‘average childhood TSH’ score was computed by averaging participants’ TSH values from 1 month of age to their current age at testing (see Figure 3.2 for an illustration of CH participants’ TSH values across infancy and childhood). As shown in Table 3.1, the average childhood TSH
value in children with CH was above the normal range of 0.4 to 4.1 mU/L (i.e., 65% of CH participants had an elevated average childhood TSH value), indicating that most CH participants were not adequately treated throughout infancy and childhood and, thus, may have experienced some prolonged periods of mild TH deficiency. All mothers of the HYPO group were hypothyroid during pregnancy and received TH treatment. Maternal TSH values were the highest during the first trimester, most likely due to inadequate TH treatment during the first half of gestation. These data indicate that most HYPO participants experienced significant TH deficiency in the first half of gestation and milder TH deficiency in the second half of gestation. Finally, the majority of HYPO participants (N = 21) had newborn TSH values within the normal range, confirming that they experienced a prenatal, but not a postnatal, period of TH deficiency.

3.3.2 Demographic and Clinical Neuropsychological Test Results

Demographic data are presented in Table 3.2. Three CH participants and one HYPO participant had a learning disability and two CH and three HYPO participants had ADHD. No significant group differences were found in sex distribution or SES. CH participants, however, had a higher mean age, $F(2,76) = 4.73; p = .012; \eta^2_p = 0.11$, and lower IQ scores, $F(2,74) = 7.03; p = .002; \eta^2_p = .16$, than controls and HYPO. For the clinical neuropsychological memory tests, groups did not differ in verbal episodic memory ($p = .144; \text{CMS Stories}$), general semantic memory ($p = .362; \text{WISC Information}$), or everyday memory ($p = .130; \text{EMQ}$). However, a trend-level group effect was found for delayed visuospatial memory on the Rey-O, $F(2,71) = 2.65; p = .078; \eta^2_p = .07$. Post-hoc ANCOVAs revealed that CH had significantly lower delayed visuospatial memory scores than controls, $F(1,49) = 4.63; p = .036; \eta^2_p = .09$, and at a trend-level, lower delayed visuospatial memory scores than HYPO, $F(1,42) = 3.62; p = .064; \eta^2_p = .08$.

3.3.3 Group Differences in AM Performance in the Recall Condition
Preliminary analyses revealed that CH and HYPO participants did not differ significantly from one another on any of AM variables in the Recall or Recall + Specific Probe conditions ($p$s $> .05$). Thus, to gain statistical power for group comparisons, both groups were collapsed into a single TH-deficient group for all analyses of AM, which was compared to controls (Note: significant group differences were evident before the two TH-deficient groups were collapsed). However, individual group means are presented in all figures of AM data (e.g., Figures 3.3-3.6).

First, group differences in total episodic and total non-episodic details in the Recall condition were examined. Results from the mixed-factor ANCOVA indicated a significant effect of group, $F(1,74) = 12.30; p = .001; \eta_p^2 = 0.14$, as well as a significant interaction between group and episodic/non-episodic detail category, $F(1,74) = 12.84; p = .001; \eta_p^2 = 0.15$. Post-hoc ANCOVAs indicated that controls recalled significantly more episodic details than the TH-deficient group, $F(1,74) = 12.57; p = .001; \eta_p^2 = 0.15$, but groups did not differ in the number of total non-episodic details recalled ($p = .300$; see Figure 3.3a for group means).

Next, group differences in the episodic detail subcategories (i.e., event, place, time, perceptual, and emotion/thought details) were examined in the Recall condition. Results from the mixed-factor ANCOVA indicated a significant main effect of group, $F(1,74) = 11.73; p = .001; \eta_p^2 = 0.14$, as well as a significant group-by-episodic detail subcategory interaction, $F(1,74) = 8.64; p = .002; \eta_p^2 = 0.11$. Post-hoc ANCOVAs indicated that controls recalled significantly more event details, $F(1,74) = 10.17; p = .002; \eta_p^2 = 0.12$, and perceptual details, $F(1,74) = 7.55; p = .008; \eta_p^2 = 0.09$, than the TH-deficient group (see Figure 3.4a for group means). Finally, group differences in the non-episodic detail subcategories (i.e., semantic details, repetitions, and other statements) were also examined using mixed-factor ANCOVA. However, no significant effects were found, indicating that both control and TH-deficient groups recalled a similar number of details within each non-episodic subcategory (see Figure 3.5a for group means).
3.3.4 Group Differences in AM Performance in the Recall + Specific Probe Condition

Group differences in total episodic and total non-episodic details were also examined in the cumulative Recall + Specific Probe condition after the provision of retrieval support. Results from the mixed-factor ANCOVA indicated a significant effect of group, $F(1,74) = 8.29; p = .005; \eta^2_p = 0.10$, as well as a significant group by episodic/non-episodic detail category interaction, $F(1,74) = 8.88; p = .004; \eta^2_p = 0.11$. Post-hoc ANCOVAs indicated that controls recalled significantly more episodic details than the TH-deficient group, $F(1,74) = 9.16; p = .003; \eta^2_p = 0.11$; however, groups did not differ in the number of total non-episodic details recalled ($p = .111$; see Figure 3.3b for group means).

Next, group differences in the specific episodic detail subcategories were examined using a mixed-factor ANCOVA. Results indicated a significant main effect of group, $F(1,74) = 9.34; p = .003; \eta^2_p = 0.11$, as well as a significant group-by-episodic detail subcategory interaction, $F(1,74) = 5.68; p = .007; \eta^2_p = 0.07$. Post-hoc ANCOVAs indicated that controls recalled significantly more event details, $F(1,74) = 7.34; p = .008; \eta^2_p = 0.09$, perceptual details, $F(1,74) = 7.07; p = .010; \eta^2_p = 0.09$, and time details, $F(1,74) = 4.34; p = .041; \eta^2_p = 0.06$, than the TH-deficient group (see Figure 3.4b for group means). Importantly, when the perceptual detail subcategory was further subdivided into visual and non-visual details, a significant group difference was found for visual details, $F(1,74) = 15.09, p < .001; \eta^2_p = 0.17$, but not for non-visual details ($p = .336$; see Figure 3.6 for group means), indicating that controls recalled significantly more visual details from past events than the TH-deficient group.

Group differences in each of the non-episodic detail subcategories were also examined using mixed-factor ANCOVA; however, no significant effects were found (see Figure 3.5b for group means). Finally, group differences in the experimenter rating composite (reflecting the
overall quality of episodic AM) and the time integration rating (reflecting the ability to integrate AMs into a larger time scale or life history) were examined using ANCOVAs. Results indicated a significant group difference in the experimenter rating composite, $F(1,74) = 4.58, p = .036; \eta^2_p = 0.06$, but not in the time integration rating ($p = .119$). Controls received higher experimenter rating scores for the overall quality of their AMs than did the TH-deficient group.

3.3.5 Group Differences in Visualization Ratings and its Effects on Episodic AM

No significant group differences were found in participants’ self-report ratings of their ability to visualize each AM at the time of recollection ($p = .250$). When hierarchical linear regressions were used to determine whether participants’ visualization ratings predicted the total number of episodic details or visual details recalled in the Recall + Specific Probe condition, no significant effects were found ($ps > .05$).

3.3.6 Group Differences in Hippocampal Volumes and its Effect on Episodic AM

Group means and standard deviations for hippocampal and intracranial volumes are presented in Table 3.3. All groups showed smaller left than right hippocampal volumes consistent with previous studies (Giedd et al., 1996; 1999; Pfluger et al., 1999; Pruessner et al., 2001), as well as larger posterior than anterior hippocampal volumes, possibly because our measurement of the posterior section included both the hippocampal body and tail, whereas the anterior measurement included only the hippocampal head. No significant group differences were found in intracranial volume ($p = .972$). For group differences in hippocampal volumes, results from the mixed-factor ANCOVA revealed only a significant main effect of group $F(2,66) = 4.05; p = .022; \eta^2_p = 0.11$, indicating that groups differed across all hippocampal sub-regions. Post-hoc ANCOVAs showed that HYPO had significantly smaller total hippocampal volumes than controls, $F(1,45) = 7.88; p = .007; \eta^2_p = 0.15$, and at a trend level, smaller total hippocampal volumes than CH, $F(1,37) = 3.16; p = .084; \eta^2_p = 0.08$. The CH group did not differ from controls in total hippocampal
volumes \((p = .624)\) after controlling for covariates. Finally, hierarchical linear regression was used to determine whether total hippocampal volumes predicted total episodic details in the Recall + Specific Probe condition; however, no significant main effect of total hippocampal volume and no significant group-by-total hippocampal volume interactions were found \((ps > .05)\).

### 3.3.7 Effects of TH Deficiency Severity on Hippocampal Volumes, Clinical Memory Scores, and Episodic AM

First, hierarchical linear regressions were used to examine whether TH deficiency severity predicted hippocampal volumes. For the HYPO group, higher maternal TSH levels (i.e., more severe TH deficiency) during the third trimester predicted smaller right anterior hippocampal volumes, \(\triangle F(1,10) = 7.99; \triangle R^2 = 0.41; B = -.670, p = .018\) (see Figure 3.7a). However, this result appeared to be entirely driven by one HYPO participant who had the most severe TH deficiency and the smallest right anterior hippocampal volume within the HYPO group, but was not a significant outlier (see Appendix I for boxplots across groups for these variables). For the CH group, TSH values at birth and at diagnosis did not significantly predict total hippocampal volumes.

Next, we examined whether TH deficiency severity in CH and HYPO groups predicted total episodic details in the Recall + Specific Probe condition as well as the clinical memory scores (i.e., verbal episodic memory, general semantic memory, and delayed visuospatial memory). As shown in Figure 3.7b, in the HYPO group, higher maternal TSH levels during the third trimester significantly predicted poorer delayed visuospatial memory scores on the Rey-O, \(\triangle F(1,12) = 4.92; \triangle R^2 = 0.22; B = -.468, p = .047\). Again, however, this result was driven by one HYPO participant with the most severe case of early TH deficiency (see Appendix I for
No significant effects were found for total episodic details in HYPO or for any of the memory variables in CH.

3.4 Discussion

This study marked the first investigation of episodic and semantic AM performance in children with early TH deficiency using the newly-developed Children’s Autobiographical Interview. Relative to typically developing controls, both CH and HYPO groups exhibited weaknesses in episodic AM, but not in semantic AM or general semantic memory. This finding is consistent with the adult patient literature showing impaired episodic AM but preserved semantic memory in patients with developmental amnesia (Rosenbaum et al., 2011; Vargha-Khadem et al., 1997; 2003) or temporal lobe epilepsy (Noulhiane et al., 2007; St-Laurent et al., 2009; Viskontas et al., 2000). Thus, early TH deficiency appears to have a similar detrimental impact on episodic AM as other conditions associated with hippocampal damage and episodic AM impairment.

In addition, children with early TH deficiency were observed to have a particular weakness in recalling event details and perceptual details from past events, especially within the visual domain. Reduced generation of visual-perceptual details was found previously in St-Laurent et al.’s (2009) study of AM in adult temporal lobe epilepsy patients with significant hippocampal atrophy. Previous research on children with early TH deficiency has shown that visuospatial impairments are the most consistently observed deficits across both CH and HYPO conditions (Man et al., 1991; Mirabella et al., 2005; Oerbeck et al., 2005; Rovet, 1999). Given that both CH and HYPO conditions were also associated with poor delayed visuospatial memory in the present study (i.e., CH has lower Rey-O scores than controls, and in HYPO, greater TH deficiency severity predicted lower Rey-O scores), our results suggest that early TH deficiency may impair the ability to encode and/or retrieve visual episodic information, which could be one factor contributing to poor recollection and re-experiencing of past events.
In order to determine whether groups may have differed in the ability to visualize past events at the time of recollection, participants’ self-report visualization ratings were examined. However, no significant group differences in visualization were found, despite the fact that groups differed in the number of visual details recalled from past events. In addition, participants’ visualization ratings did not predict episodic AM performance, contrary to the results of Study I in typically developing children. These findings suggest that children with early TH deficiency may lack insight into their particular weaknesses in episodic AM, given that adult patients with hippocampal damage also demonstrate a similar lack of insight using self-report ratings (e.g., Addis et al., 2007; Steinvorth et al., 2005). Alternatively, self-report ratings may not provide the most reliable measure of visualization abilities, particularly in clinical pediatric groups. Given that both CH and HYPO groups also showed difficulty recalling the main event details of past events, it appears that early TH deficiency may have a more general adverse impact on episodic AM recall and the ability to retrieve highly contextualized personal events.

Interestingly, CH and HYPO participants showed no significant benefit from the provision of retrieval support because they exhibited similar weaknesses in episodic AM across both Recall and Recall + Specific Probe conditions. This finding is consistent with our results in typically developing children from Study I as well as the results of other studies that have used Levine et al.’s (2002) Autobiographical Interview in adult patients with hippocampal damage (Rosenbaum et al., 2008; Steinvorth et al., 2005; St-Laurent et al., 2009). Given that this form of retrieval support has been previously shown to benefit patients with prefrontal dysfunction who have difficulty engaging in strategic retrieval operations (McKinnon et al., 2008; Svoboda et al., 2002), our results suggest that the episodic AM weaknesses observed in children with early TH deficiency may be more associated with poor hippocampal functioning than prefrontal
dysfunction. Contrary to the results found in patients with severe hippocampal damage (e.g., cases of developmental amnesia or temporal lobe epilepsy), CH and HYPO participants were not significantly impaired in other forms of memory that rely on the hippocampus, such as verbal episodic memory and everyday memory. One explanation of this finding may be the fact that both children with CH and mothers of HYPO received TH treatment, which may have lessened the severity of their TH deficiency and resulted in more subtle memory weaknesses that were only evident using particularly sensitive measures of real-world memory abilities, such as the CAI. On the other hand, episodic AM may be particularly sensitive to hippocampal damage such that even very mild hippocampal abnormalities can result in impaired episodic AM recall.

The present study was also the first to directly compare hippocampal volumes across both CH and HYPO groups. Interestingly, bilateral reductions in total hippocampal volume were found in HYPO, but not CH. This finding corresponds with animal models of early TH deficiency suggesting that early prenatal TH deficiency may have a more significant impact on hippocampal structure than late prenatal or postnatal TH deficiency (Ausó et al., 2004; Hasegawa et al., 2010; Lavado-Autric et al., 2003; Madeira et al., 1992). However, the lack of hippocampal volume reductions in CH is inconsistent with a previous study from our lab that found significantly reduced volumes (albeit only in the left hippocampus) in a larger sample of children with early-treated CH (N = 35; at p < .05; Wheeler et al., 2011). It is possible that hippocampal volume reductions in both CH and HYPO would be evident in future studies using larger samples of CH and HYPO groups. However, the results from the present study and from animal models of early TH deficiency suggest that greater reductions in hippocampal volume should be evident in HYPO than CH. Our results also showed that within the HYPO group, more severe TH deficiency during the third trimester was associated with smaller anterior hippocampal volumes and poorer delayed visuospatial memory. Interestingly, Berbel et al. (2010) also found
that TH deficiency during the third trimester, which is associated with both CH and HYPO conditions, resulted in abnormal neural migration within the anterior hippocampus, as well as poor learning and memory performance, in rats. Thus, our findings suggest that late prenatal TH deficiency could specifically impair the development of the anterior hippocampus and this may contribute to the episodic AM and visuospatial impairments observed in CH and HYPO groups. However, this warrants further investigation.

It is important to note that the hippocampal volume reductions in the HYPO group were quite small (i.e., an 8% reduction relative to controls) compared to those observed in patients with developmental amnesia who sustained more severe hippocampal damage in early life (e.g., 20-50% volume reductions; Vargha-Khadem et al., 1997; 2003). This finding of only mild hippocampal volume reductions in children with early TH deficiency may be one explanation for why only subtle memory weaknesses were observed in this population relative to the more severe episodic memory deficits observed in other patient groups. Indeed, our results are more consistent with a study by Isaacs et al. (2000) examining memory ability in children who were born prematurely and thus deprived of maternal TH contribution in late gestation. These children exhibited mild bilateral reductions (i.e., by 8-10%) in hippocampal volume and a significant impairment in everyday memory, but showed normal verbal episodic memory, delayed visuospatial memory, and semantic memory performance (Isaacs et al., 2000).

Although the present study provides critical new insight into the effects of early TH deficiency on episodic AM and hippocampal structure, it is limited for several reasons. First, we were not able to verify the details of each AM in order to assess the accuracy of participants’ AM recollections. Study III, which investigated AM accuracy in children with early TH deficiency using a staged event, was designed and conducted in order to address this limitation. Second, early TH deficiency impairs fundamental neurobiological processes within other brain regions.
that are part of the AM neural network, such as the cerebral cortex, thalamus, and cerebellum (Bernal & Nunez, 1995; Chan & Rovet, 2003). Although the hippocampus plays a critical role in episodic AM and is particularly vulnerable to TH deficiency, damage to these other regions may have also contributed to the episodic AM and visuospatial weaknesses observed in children with early TH deficiency. For example, damage to the visual cortex could have impaired the ability to encode and/or retrieve visual details from past events (Rubin & Greenberg, 1998). Thus, any conclusions based on our results should be interpreted with this in mind. Third, due to difficulties in recruiting participants, our groups were not perfectly age-matched and CH participants were significantly older than HYPO and control participants. While this difference could account for why hippocampal volumes did not differ between CH and controls (despite the fact that we controlled for age), further analyses using only age- and gender-matched CH (N = 16) and controls (N = 16) from the present study revealed no significant group differences in total hippocampal volumes. Finally, a few CH participants had missing TSH values from their health records and several mothers of the HYPO group were not consistently tested for TSH during their entire pregnancy. Thus, the analyses among TSH levels, hippocampal volumes, and memory ability did not involve the full set of cases, which may have reduced the ability to detect more significant relations among these variables, particularly within the CH group. On a similar note, our results indicating that greater severity of TH deficiency predicted smaller hippocampal volumes and poorer delayed visuospatial memory in the HYPO group (see Figure 3.7) were driven by one HYPO participant who had the most severe TH deficiency, the smallest right anterior hippocampal volume, and lowest delayed visuospatial memory score within the HYPO group, but was not a significant outlier. Although this participants’ data may accurately reflect the effects of severe TH deficiency on hippocampal volume and memory function, these results should be interpreted with caution and require further replication.
Taken together, the present study indicates that early TH deficiency is associated with weaknesses in episodic AM, but preserved semantic AM. In particular, both CH and HYPO groups exhibited difficulties in recalling event and visual details from past events. Reduced hippocampal volumes were only found in the HYPO group, which is consistent with animal research suggesting that early prenatal TH deficiency due to maternal hypothyroidism may have the most detrimental impact on hippocampal structure (Ausó et al., 2004; Hasegawa et al., 2010; Lavado-Autric et al., 2003; Madeira et al., 1992). In addition, hippocampal volumes were not found to be associated with episodic AM recall performance in either children with early TH deficiency or typically developing controls. Given that volumetric measurements provide little insight into hippocampal function, further investigations using functional MRI are required in order to investigate how early TH deficiency affects hippocampal activation during episodic AM retrieval. For example, animal studies have shown that both prenatal and postnatal TH deficiency are associated with impaired synaptic function that leads to similar memory deficits, despite being associated with different patterns of structural damage within the hippocampus (Ausó et al., 2004; Gilbert & Paczowski, 2003; Liu et al., 2010; Reid et al., 2007). Thus, episodic AM weaknesses in children with early treated TH deficiency may be the result of impaired synaptic functioning and altered neural circuitry within the hippocampus. Study IV, which examined hippocampal function during AM retrieval in children with early TH deficiency, was conducted in order to examine this issue.
Table 3.1

*Group Means and Standard Deviations (in Parentheses) for Early Thyroid Stimulating Hormone (TSH) Values and Thyroid Hormone (TH) Treatment Values for CH and Mothers of HYPO*

<table>
<thead>
<tr>
<th></th>
<th>CH (N = 26)</th>
<th>HYPO (N = 23)</th>
</tr>
</thead>
<tbody>
<tr>
<td>TH treatment dose during pregnancy (mcg/day)(^a)</td>
<td>--</td>
<td>103.57 (41.70)</td>
</tr>
<tr>
<td>Trimester 1 TSH value (mU/L)(^b)</td>
<td>--</td>
<td>9.57 (6.46)</td>
</tr>
<tr>
<td><em>(Normal range during pregnancy &lt; 2.5 mU/L)</em></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Trimester 2 TSH value (mU/L)(^c)</td>
<td>--</td>
<td>6.64 (8.64)</td>
</tr>
<tr>
<td>Trimester 3 TSH value (mU/L)(^d)</td>
<td>--</td>
<td>3.80 (4.63)</td>
</tr>
<tr>
<td>Newborn TSH value (mU/L)(^e)</td>
<td>146.74 (74.88)</td>
<td>4.06 (2.68)</td>
</tr>
<tr>
<td><em>(Normal range = 0.4-4.1 mU/L)</em></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TSH value at diagnosis (mU/L)(^f)</td>
<td>333.66 (289.96)</td>
<td>--</td>
</tr>
<tr>
<td>T4 value at diagnosis (nmol/L)(^g)</td>
<td>72.26 (75.16)</td>
<td>--</td>
</tr>
<tr>
<td><em>(Normal range = 50-150 nmol/L)</em></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age at diagnosis (in days)(^h)</td>
<td>12.32 (5.92)</td>
<td>--</td>
</tr>
<tr>
<td>Starting TH treatment dose (mcg/day)(^i)</td>
<td>41.67 (15.72)</td>
<td>--</td>
</tr>
<tr>
<td>Average childhood TSH value (mU/L)(^j)</td>
<td>8.06 (4.97)</td>
<td>--</td>
</tr>
</tbody>
</table>

Note: TSH = Thyroid Stimulating Hormone; higher TSH levels indicate more severe TH Deficiency; T4 = Thyroxine; \(^a\) 9 missing cases, \(^b\) 4 missing cases; 95% of cases were elevated above 2.5 mU/L, \(^c\) 5 missing cases; 78% of cases were elevated above 2.5 mU/L, \(^d\) 7 missing cases; 56% of cases were elevated above 2.5 mU/L, \(^e\) 6 missing CH cases and 7 missing HYPO cases (note: newborn TSH values for HYPO are from the newborn, not the mother), \(^f\) 2 missing cases, \(^g\) 6 missing cases, \(^h\) 1 missing case, \(^i\) 2 missing cases, \(^j\) 2 missing cases
### Table 3.2

*Frequency Scores, Group Means, and Standard Deviations (in Parentheses) for Demographic and Clinical Neuropsychological Measures*

<table>
<thead>
<tr>
<th></th>
<th>Controls (N = 30)&lt;sup&gt;a&lt;/sup&gt;</th>
<th>CH (N = 26)&lt;sup&gt;b&lt;/sup&gt;</th>
<th>HYPO (N = 23)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Learning Disability</td>
<td>0</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>Diagnosis of ADHD</td>
<td>0</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Sex (number of males)</td>
<td>12</td>
<td>11</td>
<td>14</td>
</tr>
<tr>
<td>SES</td>
<td>51.57 (10.19)</td>
<td>49.00 (9.91)</td>
<td>49.28 (9.83)</td>
</tr>
<tr>
<td>Age</td>
<td>10.30 (0.99)</td>
<td>11.00 (1.44)</td>
<td>10.13 (0.55)</td>
</tr>
<tr>
<td>WASI IQ score</td>
<td>117.33 (10.97)</td>
<td>105.77 (9.61)</td>
<td>111.70 (12.15)</td>
</tr>
<tr>
<td>CMS Stories Delayed&lt;sup&gt;c&lt;/sup&gt;</td>
<td>13.40 (3.16)</td>
<td>11.75 (3.38)</td>
<td>12.17 (2.40)</td>
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<tr>
<td>WISC Information&lt;sup&gt;c&lt;/sup&gt;</td>
<td>13.18 (3.22)</td>
<td>11.50 (2.30)</td>
<td>12.17 (3.68)</td>
</tr>
<tr>
<td>Rey-O Delayed</td>
<td>15.44 (5.75)</td>
<td>11.63 (7.55)</td>
<td>15.23 (6.38)</td>
</tr>
<tr>
<td>EMQ Composite</td>
<td>7.09 (1.30)</td>
<td>7.16 (1.63)</td>
<td>7.94 (1.72)</td>
</tr>
<tr>
<td>Retention Interval</td>
<td>1.20 (0.71)</td>
<td>1.10 (0.82)</td>
<td>1.04 (0.64)</td>
</tr>
</tbody>
</table>

Note: WASI = Wechsler Abbreviated Scale of Intelligence; CMS = Children’s Memory Scale, WISC = Wechsler Intelligence Scale for Children, Rey-O = Rey-Osterrieth Complex Figure task, EMQ = Everyday Memory Questionnaire (note: higher scores signify poorer performance).<sup>a</sup>7 controls did not complete the WISC; <sup>b</sup>3 CH did not complete CMS Stories, Rey-O, or the EMQ and 14 CH did not complete the WISC; <sup>c</sup>Results are expressed in scaled scores.
Table 3.3

*Group Means and Standard Deviations (in Parentheses) for Intracranial Volumes and Hippocampal Volumes*

<table>
<thead>
<tr>
<th></th>
<th>Controls (N = 30)</th>
<th>CH (N = 22)</th>
<th>HYPO (N = 20)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intracranial volume (mm$^3$)$^a$</td>
<td>1734.49 (142.15)</td>
<td>1730.01 (170.60)</td>
<td>1724.32 (177.87)</td>
</tr>
<tr>
<td>Total hippocampus (mm$^3$)</td>
<td>3894.55 (465.27)</td>
<td>3835.93 (422.80)</td>
<td>3553.48 (472.12)</td>
</tr>
<tr>
<td>Right hippocampus (mm$^3$)</td>
<td>1989.07 (252.21)</td>
<td>1957.36 (225.18)</td>
<td>1823.34 (251.31)</td>
</tr>
<tr>
<td>Right posterior (mm$^3$)</td>
<td>1056.99 (153.44)</td>
<td>1021.76 (109.02)</td>
<td>972.94 (180.29)</td>
</tr>
<tr>
<td>Right anterior (mm$^3$)</td>
<td>932.08 (168.18)</td>
<td>935.90 (197.89)</td>
<td>850.33 (175.40)</td>
</tr>
<tr>
<td>Left hippocampus (mm$^3$)</td>
<td>1905.62 (227.18)</td>
<td>1878.75 (211.87)</td>
<td>1737.81 (223.32)</td>
</tr>
<tr>
<td>Left posterior (mm$^3$)</td>
<td>1027.52 (165.07)</td>
<td>1031.03 (116.79)</td>
<td>987.77 (155.23)</td>
</tr>
<tr>
<td>Left anterior (mm$^3$)</td>
<td>878.09 (172.15)</td>
<td>847.72 (216.31)</td>
<td>750.05 (159.04)</td>
</tr>
</tbody>
</table>

$^a$Expressed per 1000 mm$^3$; Note: hippocampal volumes reflect group means after controlling for age, sex, and intracranial volume.
Figure 3.1

Manual Tracings of Anterior (White) and Posterior (Dark Gray) Subregions of the Left and Right Hippocampus Using ANALYZE 9.0 Software
Figure 3.2

*Individual TSH Levels from One Month of Age to the Current Age of Testing in Children with Congenital Hypothyroidism (N = 25)*

The dashed horizontal lines indicate the normal range for thyroid stimulating hormone (TSH) values in non-hypothyroid individuals, which is between 0.4 and 4.1 mU/L. Any score above 4.1 mU/L signifies TH deficiency. When TSH values were averaged across this time period (i.e., from one month of age to the current age of testing), 65% of cases had an average TSH value above the normal range, indicating that many CH participants experienced a prolonged period of TH deficiency and inadequate TH treatment that during infancy and childhood.
Figure 3.3

*Group Means for the Number of Total Episodic and Total Non-Episodic Details Recalled Across the Two Conditions: Recall (a) and Recall + Specific Probe (b)*

a)

![Graph showing recall results](image)

Note: error bars indicate standard error of the mean; group means reflect values after controlling for age, sex, and retention interval
Figure 3.4

Group Means for the Number of Details Recalled in Each Episodic Detail Subcategory Across the Two Conditions: Recall (a) and Recall + Specific Probe (b)

a) Recall

<table>
<thead>
<tr>
<th>Type of Episodic Detail</th>
<th>Event</th>
<th>Place</th>
<th>Time</th>
<th>Perceptual</th>
<th>Emotion &amp; Thought</th>
</tr>
</thead>
<tbody>
<tr>
<td>Recall Controls</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Recall CH</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Recall HYPO</td>
<td></td>
<td></td>
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<td></td>
</tr>
</tbody>
</table>

Note: error bars indicate standard error of the mean; group means reflect values after controlling for age, sex, and retention interval

b) Recall + Specific Probe

<table>
<thead>
<tr>
<th>Type of Episodic Detail</th>
<th>Event</th>
<th>Place</th>
<th>Time</th>
<th>Perceptual</th>
<th>Emotion &amp; Thought</th>
</tr>
</thead>
<tbody>
<tr>
<td>Controls</td>
<td></td>
<td></td>
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<td></td>
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<tr>
<td>CH</td>
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<td></td>
</tr>
<tr>
<td>HYPO</td>
<td></td>
<td></td>
<td></td>
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<td></td>
</tr>
</tbody>
</table>

Note: error bars indicate standard error of the mean; group means reflect values after controlling for age, sex, and retention interval
Figure 3.5

Group Means for the Number of Details Recalled from Each Non-Episodic Detail Subcategory Across the Two Conditions: (a) Recall and (b) Recall + Specific Probe

a)

Recall

![Graph showing recall for different subcategories and conditions]

b)

Recall + Specific Probe

![Graph showing recall with specific probe for different subcategories and conditions]

Note: error bars indicate standard error of the mean; group means reflect values after controlling for age, sex, and retention interval
Figure 3.6

*Group Means for the Number of Visual and Non-Visual Details Recalled in the Recall + Specific Probe Condition*

Note: error bars indicate standard error of the mean; group means reflect values after controlling for age, sex, and retention interval
Figure 3.7

Scatterplots of Maternal TSH Values During the Third Trimester by Right Anterior Hippocampal Volumes (a) and Delayed Visuospatial Memory Scores (b) in the HYPO Group

a)

```
TSH x Right Anterior Hippocampal Volume Scatterplot in HYPO
```

b)

```
TSH x Delayed Visuospatial Memory Scatterplot in HYPO
```

Note: each graph depicts raw values before accounting for covariates; Rey-O = Rey-Osterrieth Complex Figure task; TSH = thyroid stimulating hormone
Chapter 4
Study III: Accuracy of Episodic Autobiographical Memory in Children with Early Thyroid Hormone Deficiency Using a Staged Event

4.1 Introduction

Episodic autobiographical memory (AM), or the recollection of specific past events, is a highly re-constructive cognitive process involving the integration of many different types of episodic details (e.g., spatial, temporal, visual, emotional, etc.; Svoboda et al., 2006). A large number of AM studies have focused on measuring the total number of episodic details individuals report about past events, with a greater quantity of details signaling better episodic AM performance (e.g., Levine et al., 2002; St-Laurent et al., 2009). Although this method has many advantages, it may not provide the most sensitive measure of children’s episodic AM performance if it does not involve verifying original event details or controlling for total verbal output (Koriat & Goldsmith, 1994). For example, some children may report a greater number of episodic details about past events than others simply because they have more developed language abilities and thus, have greater verbal output. In addition, other children may report a large number of inaccurate episodic details during memory interviews because they may feel pressure to provide a response when asked probing questions, despite being unsure of their response (Roebers & Schneider, 2000). It is well-known that AMs often contain errors and are not completely accurate representations of past events (Hyman & Loftus, 1998). Thus, several researchers have suggested that measures of AM accuracy that also control for total verbal output may provide a more sensitive measure of children’s episodic AM ability than the total number of episodic details children can report about past events (e.g., Koriat & Goldsmith, 1994).

One promising technique for assessing AM accuracy is the use of staged autobiographical events (i.e., demonstrations or activities where the content or details are controlled). For example Bruck, London, Landa, and Goodman (2007) had children participate in a staged magic show,
and at a later date, the authors assessed the accuracy of the children’s recollections of this event. This staged event technique is beneficial because it allows for the independent verification of original event details and it reduces variability across participants’ recollections because all participants experience the same autobiographical event (Bruck et al., 2007). Studies that have previously used staged events to examine AM accuracy in clinical pediatric populations, such as children with autism or intellectual disability, have shown that after controlling for total verbal output, these groups provide proportionally less accurate recollections of past events than their typically developing peers (Agnew & Powell, 2004; Bruck et al., 2007). Thus, the use of staged events may provide an important avenue for investigating AM accuracy in children who exhibit abnormal development of the hippocampus, which is a critical brain structure for episodic AM retrieval (Eldridge et al., 2000; Moscovitch, 2008).

Recent advances in neuroimaging techniques have also prompted significant interest in AM accuracy, specifically examining whether the hippocampus is preferentially activated during accurate or successful episodic AM retrieval. Although regions within the prefrontal cortex (e.g., dorsolateral and ventrolateral prefrontal regions) play an essential role in monitoring and verifying retrieved information, the hippocampus is also important for accurate AM retrieval because it mediates retrieval processes supported by the prefrontal cortex and reintegrates episodic details linked together in a memory trace (Addis et al., 2007; Brassen, Weber-Fahr, Sommer, & Lehmbeck, 2006; Cabeza et al., 2004; Kircher et al., 2008; Skinner, Fernandes, & Grady, 2009). For example, Cabeza et al. (2004) recently examined AM retrieval accuracy using a novel photo paradigm that controlled for the content of participants’ AMs. Cabeza et al. (2004) found significant activation within the hippocampus, medial prefrontal cortex (i.e., involved in self-referential processing), and parahippocampal gyrus (i.e., involved in visuospatial memory) during correct recognition trials, indicating that the hippocampus is involved in accurate AM
retrieval. Other neuroimaging studies examining episodic recognition memory have found similar results, in that retrieval success (or accuracy) was associated with robust activity in the hippocampus and medial temporal lobe (e.g., Eldridge et al., 2000; Montaldi et al., 2001; Stark & Squire, 2000). In addition, several studies have reported that the anterior hippocampus appears to be especially important for successful episodic encoding and retrieval (Kircher et al., 2008; Sperling et al., 2003). Given evidence suggesting that the hippocampus plays an important role in accurate episodic encoding and retrieval, it is possible that individuals with early hippocampal damage may have difficulty recalling accurate episodic AM details from a staged event. However, no study to date has used a staged event to examine AM accuracy in children with hippocampal abnormalities.

The main goal of the present study was to investigate AM accuracy in children who experienced early TH deficiency, which is known to have to adverse effects on hippocampal structure and function (Gilbert & Paczowski, 2003; Lavado-Autric et al., 2003). In particular, AM accuracy was examined in two populations with early TH deficiency: (a) children of treated hypothyroid women (HYPO), who were exposed to insufficient maternal TH levels throughout gestation, with greater severity of TH deficiency during the first half of gestation; and (b) children with early-treated congenital hypothyroidism (CH), who experienced late prenatal and postnatal TH deficiency due to fetal thyroid gland dysfunction (Zoeller & Rovet, 2004). Both of these populations exhibit weaknesses in episodic AM recall (i.e., shown in Study II) as well as reduced hippocampal volumes relative to typically developing controls (i.e., shown in Study II for HYPO and Wheeler et al., 2011, for CH). In order to assess AM accuracy, a staged autobiographical event was developed and participants’ recollections of the staged event were subsequently assessed using the newly-developed Children’s Autobiographical Interview. The primary variable of interest in the present study was proportion accuracy scores (i.e., the
percentage of total episodic details that were accurately recalled), in order to control for total verbal output and any possible group differences in language ability. Based on the results of previous studies examining AM accuracy in other clinical pediatric populations, it was expected that both CH and HYPO groups would exhibit proportionally less accurate recollections of the staged event than typically developing controls.

Given that the hippocampus is a critical structure for both episodic AM recall and accuracy, a secondary goal of the present study was to determine whether total hippocampal volumes predicted AM accuracy performance (i.e., proportion accuracy scores) and/or episodic AM recall performance (i.e., total episodic details reported) in children with early TH deficiency and typically developing controls. Based on our findings from Study II, showing that hippocampal volumes did not predict total episodic details, and the fact that proportion accuracy scores may provide a more sensitive measure of children’s episodic AM and hippocampal function than the total number of episodic details reported, we expected to find significant relations only between proportion accuracy scores and hippocampal volumes. In particular, we hypothesized that smaller hippocampal volumes in children with early TH deficiency would predict lower proportion accuracy scores. Finally, in order to investigate whether children who experienced more severe TH deficiency exhibited poorer AM accuracy performance, we also examined the relation between proportion accuracy scores and elevated thyroid stimulating hormone (TSH) values during gestation for HYPO (i.e., maternal TSH values) and at birth/diagnosis for CH.

4.2 Methods

4.2.1 Participants

Seventy-four children (46% male) between the ages of 10 and 14 years ($M = 10.64; SD = 1.15$) were recruited for the present study. The sample included 25 children with CH, 21 HYPO, and
28 typically developing controls. The majority (N = 70) had participated in Study II (which was run concurrently with Studies III and IV), while an additional 4 participants (3 CH, 1 CON) were recruited from a separate ongoing study in our lab. All CH participants except two were identified at birth through the Ontario newborn screening program, which uses a thyroid stimulating hormone (TSH) test to screen for hypothyroidism (see Table 4.1 for TSH values in CH). The exceptions were two males born outside of Canada, one diagnosed at 15 days of age and one who was not formally diagnosed until 2 years of age but did not exhibit dramatically elevated TSH value at diagnosis (i.e., his TSH value at diagnosis was 10 mU/L). The CH group consisted of eight children with athyrosis (i.e., an absent or dysfunctional thyroid gland), 13 with ectopic or lingual glands (i.e., an abnormally located thyroid gland), two with dyshormonogenesis (i.e., a defect in TH synthesis), and two with unknown etiologies. All CH participants had elevated TSH values at birth or at diagnosis. The entire HYPO group belonged to a cohort recruited at birth and followed throughout childhood at SickKids. Mothers of the HYPO group were originally identified through the SickKids’ Motherisk program or through local endocrinologists. All mothers of the HYPO group were hypothyroid during pregnancy and received TH treatment. Maternal TSH values were the highest during the first trimester, most likely due to inadequate TH treatment during the first half of gestation (see Table 4.1 for maternal TSH values). Finally, all controls were recruited from a list of past participants of which 25 were from the longitudinal cohort.

Exclusionary criteria were identical to Study II. Two controls were excluded from the analyses, one with an identified learning disability and one with a diagnosis of ADHD. Four HYPO participants were excluded from the analyses, one for a neuroradiological abnormality (i.e., a frontal dysembryoplastic neuroepithelial tumor) and three because their mothers’ TSH values were within a normal range throughout pregnancy. Thus, the remaining sample of
participants consisted of 68 children (46% male) between the ages of 10 and 14 years ($M = 10.71$, $SD = 1.17$) and included 25 CH, 17 HYPO, and 26 controls. Within this sample, four participants did not complete the structural imaging portion of the study because they did not want to undergo scanning (2 CH, 1 HYPO), or moved so excessively during the scan that their data had to be discarded (1 CH). All participants were fluent or native English speakers. Family Hollingshead SES scores (Hollingshead, 1975) ranged from 26 to 76 ($M = 50.24$, $SD = 10.25$), including 5% in the medium-low income range, 10% in the medium income range, 51% in the medium-high income range, and 34% in the high income range.

4.2.2 General Procedure

All parents provided written consent for participation in this study while participants also provided verbal assent. Participants were individually tested in the Psychology Department at SickKids over the course of two days, separated by four and a half months ($M = 4.60; SD = 2.37$). On Day 1, participants took part in a clinical neuropsychological assessment of their intelligence (and general memory ability, which was assessed in Study II), while parents completed several questionnaires. Participants also took part individually in a 45-minute staged event during their lunch break. At the start of the staged event, participants were given detailed instructions about the staged event (see Appendix J) as well as 10 dollars to purchase a meal for lunch. During the staged event, participants received a tour of the hospital, answered a set of standard questions (e.g., regarding the date, current location in the hospital, the weather outside, etc.), and performed a series of tasks (e.g., played 20 questions, counted footprints on the floor, identified objects in a wall display, bought a lunch, watched a video, smelt a fragrant plant, etc.). Effort was made to ensure that the staged event was experienced identically across all participants by having the examiner use scripted statements (see Appendix K for a detailed script of the staged event). In addition, the staged event was designed so that it contained enough
unique event happenings, time, place, and visual/sensory/perceptual details to be comparable to naturally occurring autobiographical events. One examiner (K.W.) performed 99% of the staged events and a second trained examiner performed the staged event for one CH participant. At the end of Day 1, participants received a certificate of participation, a movie gift certificate, and parents were compensated for transportation.

On Day 2, participants were interviewed about the staged event using the Children’s Autobiographical Interview (CAI). One examiner (K.W.) conducted 99% of the interviews, while a second trained examiner conducted one interview for a CH participant. Immediately after the CAI, participants underwent structural MRI scanning in a 1.5 Tesla Signa GE scanner, during which they viewed movies via MRI-compatible goggles in the Diagnostic Imaging Unit at SickKids. A neuroradiologist examined all MRI images for neuroradiological abnormalities and sent written reports to participants’ family physicians. At the end of Day 2, participants received a movie gift certificate and a CD containing several pictures of their own brain. Parents received compensation for transportation as well as a report describing their child’s performance on the neuropsychological assessment from Day 1. All procedures were approved by the Research Ethics Board of SickKids and the Office of Research Ethics at the University of Toronto.

4.2.3 **Demographic Information and Assessment of Intelligence**

Demographic information was obtained from all parents using the same demographic questionnaire from Study I. Intelligence was evaluated during the clinical neuropsychological assessment using the Vocabulary and Matrix Reasoning subtests of the Wechsler Abbreviated Scale of Intelligence (WASI; Wechsler, 1999), which yields an estimate of Full Scale IQ.

4.2.4 **Early TSH Levels and TH Treatment Values for CH and HYPO**
For CH participants, information on early TSH and TH treatment values were obtained from medical health records at SickKids (see Table 4.1 for missing cases). For HYPO participants, maternal TSH and TH treatment values during pregnancy were obtained from the participants’ family physicians (see Table 4.1 for missing cases).

4.2.5 *Children’s Autobiographical Interview*

Participants’ AM performance was assessed using the same Children’s Autobiographical Interview (CAI) from Study I (see Study I for a more detailed description of the CAI). However, for the present study only participants’ recollections of the staged event were assessed and additional questions about the staged event were added in the Specific Probe phase (see Appendix L for a list of these additional questions). Importantly, these additional questions were designed to limit suggestibility and required participants to provide an actual detail rather than a yes/no response. Similar to Studies I and II, participants completed all three phases of the CAI (i.e., free recall, general probe, and specific probe) for the staged event and provided a self-report rating of their ability to visualize the staged event at the time of recollection.

4.2.5.1 *Scoring Protocol for the Children’s Autobiographical Interview*

The CAI scoring protocol was similar to Study I, except that: (a) only episodic details were scored across each phase of the CAI (i.e., free recall, general probe, and specific probe) and were summed to provide a *total episodic details* composite score; (b) details from the emotion/thought subcategory were excluded from all analyses assessing accuracy because they could not be objectively deemed accurate or inaccurate, (c) details from each episodic subcategory (i.e., event, place, time, and perceptual details) were further subdivided into *inaccurate* and *accurate* detail subcategories (see below for a description), and (d) the accurate perceptual detail subcategory was further subdivided into accurate *visual* and accurate *non-visual* detail subcategories (see
Study II for further description of visual and non-visual episodic detail criteria). Inaccurate details included any reported episodic detail that was deemed incorrect based on detailed records from each participant’s staged event (see Table 4.2a for examples). The majority of inaccurate details were either approximations (i.e., imprecise details) or confabulations (i.e., completely false details; see Table 4.2a for examples). A total inaccurate details composite score was created by summing all of the details from each inaccurate episodic detail subcategory (i.e., event, place, time, and perceptual).

Accurate details referred to any reported episodic detail that was deemed correct based on detailed records of each participant’s staged event (see Table 4.2b for examples). A total accurate details composite score was created by summing all of the details from each accurate episodic detail subcategory (i.e., event, place, time, and perceptual details). Finally, in order to assess AM accuracy after controlling for total verbal output, a proportion accuracy score was created by dividing the total number of accurate details recalled by the total number of episodic details recalled (i.e., excluding emotion/thought details). All memories were scored by K.W. and then for reliability, 46% of the memories selected at random within each group (10 CH, 10 HYPO, 14 CON) were re-scored by a second extensively trained scorer. Both scorers were blind to participants’ group, age, and sex. Inter-rater reliability was determined using intra-class correlations (one-way random effects model; McGraw & Wong, 1996). Coefficients for total inaccurate details, total accurate details, and proportion accuracy scores were 0.90, 0.90, and 0.85 respectively.

4.2.6 Structural MRI Acquisition, Processing, and Hippocampal Volumes

The hippocampal volume measurements collected in Study II were also used in the present study along with additional hippocampal volume data collected from the four participants who did not participate in Study II (see Study II for a more detailed description of structural image
acquisition and processing, and manual tracing procedures). For the present study, inter-rater reliability was assessed for 36% of right and left hippocampal volumes selected at random within each group (6 CH, 7 HYPO, 8 CON). An intra-class correlation analysis using a one-way random effects model (McGraw & Wong, 1996) indicated coefficients of 0.84 (Cronbach α = 0.93) for the right hippocampus and 0.88 (Cronbach α = 0.95) for the left hippocampus.

4.2.7 Data Analysis

Similar to Study I, all details recalled in the first two phases of the CAI (i.e., free recall and general probe) were collapsed to form a single ‘Recall’ condition that was analyzed separately from the cumulative ‘Recall + Specific Probe’ condition. However, given that very few inaccurate details (M = 1.51; SD = 1.36) and few accurate details (M = 16.08; SD = 9.67), which were mainly event details, were recalled in the Recall condition, only scores from the Recall + Specific Probe condition were examined in the present study. All variables of interest were examined for outliers (i.e., > 3 SD from the mean). No outliers were found in hippocampal volumes, IQ scores, or early TSH values. However, two outliers (1 CH, 1 CON) were found in the accurate detail subcategories and these were replaced with the highest or lowest reasonable score within their particular group (i.e., CH or CON) using Winsorization (Field, 2009; Grace & Sawilowsky, 2009; Note: results were identical when outliers were not replaced). All variables of interest were also examined for deviations in skewness and kurtosis in order to assess the assumption of normality. Several TSH variables (i.e., maternal TSH values in each trimester for HYPO and average childhood TSH values for CH) exceeded the cutoffs for skewness (±2) and kurtosis (±2) and were corrected using log10 transformations. Several AM variables were significantly non-normal using the Kolmogorov-Smirnov test (see Appendix M for a list of these variables). However, parametric tests were used in the present study because the results were identical to those produced using non-parametric tests (see Appendix M for the results using
non-parametric Mann-Whitney Tests), and it was deemed important to use ANCOVA, which reduced bias by controlling for important covariates (e.g., age, sex, and retention interval) and provided effect sizes for group comparisons.

Regarding demographic variables, chi-squared tests were used to compare groups on sex distribution, and ANOVAs were used to compare groups on age (measured in years), SES, and IQ scores. Group differences in proportion accuracy scores were examined using ANCOVA, with age, sex, and retention interval as covariates. Although retention interval did not differ significantly across groups ($p = .314$; see Table 4.3 for group means and standard deviations), it was used as a covariate because it was significantly correlated with total episodic details; $r = -.377, p = .002$, total accurate details; $r = -.322, p = .007$, and all of the accurate detail subcategories ($ps < .05$). Group differences in total inaccurate and total accurate details were examined using a mixed-factor ANCOVA, with detail category (inaccurate/accurate) as the repeated measure, group as the between subjects variable, and age, sex, and retention interval as the control variables. Group differences in inaccurate and accurate details subcategories were examined using separate mixed-factor ANCOVAs with the Greenhouse-Geisser correction applied. Detail subcategory (i.e., event, place, time, perceptual) was the repeated measure, group was the between-subjects variable, and age, sex, and retention interval were the control variables. Group differences in accurate visual and non-visual details, and participants’ visualization ratings were examined using ANCOVA, controlling for age, sex, and retention interval. Hierarchical linear regressions were used to determine whether participants’ visualization ratings predicted total accurate details, accurate visual details or proportion accuracy scores. For these analyses, age, sex, and retention interval were entered as covariates in step 1, dummy-coded group and visualization ratings were entered as predictors in step 2, and dummy-coded group-by-visualization rating interaction variables were entered in step 3.
Similar to Study II, group differences in hippocampal volumes were examined using a mixed-factor ANCOVA, with hippocampal sub-region (i.e., right posterior, right anterior, left posterior, left anterior) as the repeated measure, group as the between-subjects variable, and age, sex, and intracranial volume as the control variables. In order to assess whether hippocampal volumes better predicted proportion accuracy scores than total episodic details, hierarchical linear regressions were used with age, sex, retention interval, and intracranial volumes entered as control variables in step 1, dummy-coded group variables and hippocampal volumes entered as predictors in step 2, and the dummy-coded group-by-hippocampal volume interaction variables entered in step 3. Finally, hierarchical linear regressions were also used to examine whether early TSH values in CH and HYPO predicted proportion accuracy scores after controlling for age, sex, and retention interval. Given the exploratory nature of the present study, an overall significance level of $p < .05$ was used and a few important trend-level effects (at $p < .10$) are discussed. However, effect sizes are reported and most results approached a significance level of $p < .01$.

### 4.3 Results

#### 4.3.1 Demographic Measures

Demographic data are presented in Table 4.3. Two CH participants had learning disabilities and two CH participants and one HYPO participant had ADHD. No significant group differences were found in sex distribution or SES. However, the CH group had a higher mean age, $F(2,71) = 9.73; p < .001; \eta^2_p = 0.22$, and lower IQ scores, $F(2,65) = 11.33; p < .001; \eta^2_p = .26$, than HYPO and controls.

#### 4.3.2 Group differences in AM Performance in the Recall + Specific Probe Condition

Preliminary analyses revealed that CH and HYPO participants did not differ significantly from one another on any of the AM variables in the present study ($ps > .05$). Thus, to gain statistical
power for group comparisons, both groups were collapsed into a single TH-deficient group for all analyses of AM (Note: significant group differences were evident before the two TH-deficient groups were collapsed). However, individual group means are presented in all figures of the AM data (e.g., Figures 4.1 and 4.2).

First, group differences in proportion accuracy scores were examined using ANCOVA. A significant main effect of group was found, $F(1,63) = 6.72; p = .012; \eta_p^2 = 0.10$, indicating that controls had more accurate recollections of the staged event than did the TH-deficient group after controlling for total episodic details recalled (see Figure 4.1a for group means). Next, group differences in total inaccurate and total accurate details in the Recall + Specific Probe condition were examined. Results from the mixed-factor ANCOVA revealed a trend-level main effect of group, $F(1,63) = 3.51; p = .066; \eta_p^2 = 0.05$, and a significant interaction between group and inaccurate/accurate detail category, $F(1,63) = 10.72; p = .002; \eta_p^2 = 0.15$. Post-hoc ANCOVAs indicated that controls recalled significantly more accurate details than the TH-deficient group, $F(1,63) = 6.90; p = .011; \eta_p^2 = 0.10$, but groups did not differ in the number of inaccurate details recalled ($p = .308$; see Figure 4.1b for group means).

Group differences in inaccurate episodic detail subcategories (i.e., event, place, time, and perceptual details) using a mixed-factor ANCOVA showed no significant differences between groups ($p > .300$; see Figure 4.2a for group means). However, when groups were similarly compared for differences in accurate episodic detail subcategories (i.e., event, place, time, and perceptual details), results indicated a significant main effect of group, $F(1,63) = 7.51; p = .008; \eta_p^2 = 0.11$. This finding indicates that across all subcategories of accurate episodic details, controls recalled more accurate details than the TH-deficient group (see Figure 4.2b for group means). Importantly, when the accurate perceptual detail subcategory was further subdivided into accurate visual and accurate non-visual details, a significant group difference was found for
accurate visual details, $F(1,63) = 4.77, p = .033; \eta^2_p = 0.07 (M = 11.48$ for TH-deficient group; $M = 14.46$ for controls), but not for non-visual details ($p = .478$). This finding indicates that controls recalled significantly more accurate visual details from the staged event than the TH-deficient group.

4.3.4 Group Differences in Visualization Ratings and its Effects on Episodic AM

No significant group differences were found in participants’ self-report ratings of their ability to visualize the staged event at the time of recollection ($p = .367$). Next, hierarchical linear regressions were used to determine whether participants’ visualization ratings predicted total accurate details, accurate visual details, and proportion accuracy scores from the Recall + Specific Probe condition. Results indicated a significant main effect of participants’ visualization ratings only for total accurate details, $\Delta F(3,61) = 3.99; \Delta R^2 = 0.13; B =.211; p = .048$, and accurate visual details, $\Delta F(3,61) = 4.84; \Delta R^2 = 0.17; B =.288; p = .010$. Across all participants, a greater ability to visualize the staged event at the time of recollection significantly predicted a greater number of total accurate details and accurate visual details recalled from the staged event.

4.3.5 Group Differences in Hippocampal Volumes and its Effects on Episodic AM

Group means and standard deviations for intracranial and hippocampal volumes are presented in Table 4.3. No significant group differences were found in intracranial volume ($p = .700$). As shown in Table 4.3, the HYPO group had smaller hippocampal volumes than controls and CH; however, these group differences were not significant using a mixed-factor ANCOVA (e.g., $p = .154$ for total hippocampal volumes). Hierarchical linear regressions were used to examine whether total hippocampal volumes better predicted proportion accuracy scores than total episodic details recalled (i.e., the total composite including emotion/thought details). No significant effect of total hippocampal volume was found for total episodic details. For proportion accuracy scores, however, a significant main effect of total hippocampal volume was
found, $\Delta F(3,56) = 3.63; \Delta R^2 = 0.14; B = .313; p = .023$, indicating that smaller hippocampal volumes predicted lower proportion accuracy scores in all groups. However, as shown in Figure 4.3 (i.e., scatterplots of total hippocampal volumes by proportion accuracy scores for each group), this effect appears to be driven by the CH and HYPO groups.

Given that total hippocampal volumes were found to significantly predict proportion accuracy scores, additional hierarchical linear regression analyses were conducted to examine whether particular hippocampal subregions (i.e., right posterior, right anterior, left posterior, left anterior) predicted proportion accuracy scores. Results indicated a significant main effect of left anterior hippocampal volumes on proportion accuracy scores, $\Delta F(3,56) = 3.41; \Delta R^2 = 0.14; B = .301; p = .031$, signifying that across all groups, participants with smaller left anterior hippocampal volumes had lower proportion accuracy scores. In addition, a significant interaction between right anterior hippocampal volumes and the dummy-coded group variables was found, $\Delta F(2,54) = 2.54; \Delta R^2 = 0.09; p = .031$ ($B = .346; p = .014$ for the HYPO vs. CON dummy variable; and $B = .281; p = .047$ for the CH vs. CON dummy variable). These significant interactions indicate that only in CH and HYPO groups (and not controls) did smaller right anterior hippocampal volumes significantly predict lower proportion accuracy scores.

4.3.6 Effects of TH Deficiency Severity on Proportion Accuracy Scores

As shown in Figure 4.4a, higher maternal TSH levels (signifying more severe TH deficiency) during the third trimester significantly predicted lower proportion accuracy scores in the HYPO group, $\Delta F(1,9) = 5.69; \Delta R^2 = 0.33; B = -.479, p = .041$. In the CH group, higher TSH levels (signifying more severe TH deficiency) at birth also predicted lower proportion accuracy scores at a trend-level, $\Delta F(1,24) = 3.60; \Delta R^2 = 0.10; B = -.353, p = .070$ (see Figure 4.4b).

4.4 Discussion
The present study represents the first investigation of AM accuracy in children with early TH deficiency using a staged autobiographical event. Results from the Children’s Autobiographical Interview showed that both CH and HYPO groups recalled significantly fewer accurate details and had proportionally less accurate recollections of the staged event than did typically developing controls. Although no previous study has specifically examined AM accuracy in individuals with hippocampal abnormalities, our findings are consistent with other studies investigating AM accuracy in other clinical pediatric populations, such as children with autism or intellectual disability, who report fewer episodic details and provide proportionally less accurate recollections of a staged event than controls (Agnew & Powell, 2004; Bruck et al., 2007).

Interestingly, we also found that more severe TH deficiency (i.e., in the third trimester for HYPO and at birth for CH) was associated with lower proportion accuracy scores in both CH and HYPO groups. Thus, our results suggest that late prenatal TH deficiency may have long-term consequences for the ability to accurately recall episodic details from past events.

Unlike the results from Study II showing that CH and HYPO participants had a specific weakness in recalling event and perceptual details from past events, CH and HYPO participants in the present study had difficulty recalling accurate details about the staged event across all subcategories of episodic details (e.g., event, place, time, and perceptual), including visual details. This finding suggests that early TH deficiency may lead to a general weakness in the ability to recall accurate details from past events; however, these differential results may be due to inherent differences between a staged autobiographical event and a naturally-occurring autobiographical event (see below for a description of differences between the staged event and naturally-occurring events recalled in Study II). Similar to Study II, we found no significant group differences in participants’ self-report visualization ratings despite the fact that both CH and HYPO groups recalled fewer accurate visual details than controls. However, we also found
that across all participants, greater visualization of the staged event at the time of recollection predicted a greater number of total accurate details and accurate visual details recalled, suggesting that visual imagery is an important component of accurate episodic AM retrieval.

Although HYPO participants did not exhibit significantly reduced hippocampal volumes in the present study, they did exhibit smaller volumes than CH and controls. The lack of significant group differences in hippocampal volumes in the present study may be due to our smaller sample size in the HYPO group (i.e., N = 20 for Study II, but N = 15 for Study III) and the fact that treated TH deficiency appears to have only mild effects on hippocampal volume that may be difficult to reliably detect using low resolution scanning (i.e., with 1.5T scanner). Importantly, the results indicated that smaller hippocampal volumes, particularly smaller anterior hippocampal volumes, significantly predicted lower proportion accuracy scores, especially in the CH and HYPO groups. Previous research indicates three important features of the anterior hippocampus that are relevant to our findings: (a) it plays an essential role in accurate episodic encoding and retrieval (Kircher et al., 2008), (b) it projects to the prefrontal cortex, which also plays a role in AM accuracy by verifying retrieved information (Barbas & Blatt, 1995; Kircher et al., 2008), and (c) it shows less postnatal growth than the posterior hippocampus (Gogtay et al., 2006) and therefore, may be more vulnerable to TH deficiency during gestation, which was shown in Study II. Thus, our findings suggest that reductions in anterior hippocampal volumes associated with late prenatal TH deficiency may be associated with significant weaknesses in recalling accurate episodic details from past events. In addition, because hippocampal volumes significantly predicted proportion accuracy scores but not total episodic details across all groups in the present study, our results also suggests that proportion accuracy scores, which assess only accurate AM retrieval and control for total verbal output, may be a particularly sensitive
measure of episodic AM impairment and hippocampal dysfunction in patients with hippocampal abnormalities.

Several important differences distinguishing the present study from Study II warrant discussion, given that all participants, particularly CH participants, recalled a greater number of total episodic details from the staged event ($M = 63.37; SD = 19.07$; reflecting the composite score including emotion/thought details) than from naturally occurring events reported in Study II ($M = 56.86; SD = 18.42$). For instance: (a) the staged event was more recent than events recalled in Study II, which may have made it easier to recall; (b) participants were given specific instructions to pay close attention to event and perceptual details during the staged event (see Appendix J), which may have lead to better encoding and smaller group differences within the event and perceptual subcategories of episodic details; (c) additional probing questions about the staged event were included in the present study, which may have improved recall due to the provision of additional retrieval support, (d) CH participants may have been more familiar with the surroundings at SickKids than HYPO and controls due to their annual TH checkups; however, efforts were made to use unique locations, objects, and tasks for the staged event, and both HYPO and control groups were part of a longitudinal cohort tested several times at SickKids; (e) all participants returned to the same location as the staged event for the CAI, which may have provided them with additional retrieval cues, and (f) the staged event may have been more salient and may have involved more activities, references to time and place, and objects than naturally-occurring events, allowing for more episodic details to be recalled. Despite these differences, however, significant group effects were evident in the number of accurate details recalled and proportion accuracy scores, indicating that early TH deficiency is associated with impaired episodic AM accuracy performance.
Finally, the limitations of this study are similar to those in Study II. For example, early TH deficiency impairs neurobiological processes within other regions of the brain, such as the prefrontal cortex, which could also contribute to weaknesses in AM accuracy and the ability to verify retrieved information. In addition, our groups were not perfectly age-matched and there were several missing TSH values with the CH and HYPO groups which may have biased our results. Thus, our results should be interpreted with these limitations in mind.

In conclusion, the present study was the first to indicate that children with early-treated CH and children born to women with treated hypothyroidism exhibit difficulties in recalling accurate episodic details from past events and this weakness appears to be associated with both reduced anterior hippocampal volumes and more severe TH deficiency during late gestation (i.e., the third trimester). In addition, hippocampal volumes were found to significantly predict proportion accuracy scores, but not the total number of episodic details recalled, suggesting that proportion accuracy scores may provide a more sensitive measure of children’s episodic AM ability, as well as hippocampal dysfunction, in clinical pediatric populations. However, given that hippocampal volumes provide no insight into the functional integrity of the hippocampus, additional investigations using functional MRI are required in order to examine whether early TH deficiency is specifically associated with abnormal hippocampal function during episodic AM retrieval. Thus, Study IV was specifically designed in order to examine this issue.
### Table 4.1

**Group Means and Standard Deviations (in Parentheses) for Early Thyroid Stimulating Hormone (TSH) Values and Thyroid Hormone (TH) Treatment Values for CH and Mothers of HYPO**

<table>
<thead>
<tr>
<th></th>
<th>CH (N = 25)</th>
<th>HYPO (N = 17)</th>
</tr>
</thead>
<tbody>
<tr>
<td>TH treatment dose during pregnancy (mcg/day)&lt;sup&gt;a&lt;/sup&gt;</td>
<td>--</td>
<td>97.73 (34.79)</td>
</tr>
<tr>
<td>Trimester 1 TSH value (mU/L)&lt;sup&gt;b&lt;/sup&gt; (Normal range during pregnancy &lt; 2.5 mU/L)</td>
<td>--</td>
<td>9.76 (7.23)</td>
</tr>
<tr>
<td>Trimester 2 TSH value (mU/L)&lt;sup&gt;c&lt;/sup&gt;</td>
<td>--</td>
<td>7.38 (9.31)</td>
</tr>
<tr>
<td>Trimester 3 TSH value (mU/L)&lt;sup&gt;d&lt;/sup&gt;</td>
<td>--</td>
<td>4.90 (4.67)</td>
</tr>
<tr>
<td>Newborn TSH value (mU/L)&lt;sup&gt;e&lt;/sup&gt; (Normal range = 0.4-4.1 mU/L)</td>
<td>135.00 (75.89)</td>
<td>4.54 (3.05)</td>
</tr>
<tr>
<td>TSH value at diagnosis (mU/L)&lt;sup&gt;f&lt;/sup&gt;</td>
<td>352.75 (307.24)</td>
<td>--</td>
</tr>
<tr>
<td>T4 value at diagnosis (nmol/L)&lt;sup&gt;g&lt;/sup&gt; (Normal range = 50-150 nmol/L)</td>
<td>72.21 (78.75)</td>
<td>--</td>
</tr>
<tr>
<td>Age at diagnosis (in days)&lt;sup&gt;h&lt;/sup&gt;</td>
<td>42.75 (146.50)</td>
<td>--</td>
</tr>
<tr>
<td>Starting TH treatment dose (mcg/day)&lt;sup&gt;i&lt;/sup&gt;</td>
<td>40.61 (16.69)</td>
<td>--</td>
</tr>
<tr>
<td>Average childhood TSH value (mU/L)&lt;sup&gt;j&lt;/sup&gt;</td>
<td>8.43 (5.00)</td>
<td>--</td>
</tr>
</tbody>
</table>

Note: TSH = Thyroid Stimulating Hormone; higher TSH levels indicate more severe TH Deficiency; T4 = Thyroxine; <sup>a</sup>6 missing cases, <sup>b</sup>4 missing cases; 92% of cases were elevated above 2.5 mU/L, <sup>c</sup>3 missing cases; 93% of cases were elevated above 2.5 mU/L, <sup>d</sup>3 missing cases; 64% of cases were elevated above 2.5 mU/L, <sup>e</sup>6 missing CH cases and 6 missing HYPO cases (note: newborn TSH values for HYPO are from the newborn, not the mother), <sup>f</sup>6 missing cases, <sup>g</sup>5 missing cases, <sup>h</sup>1 missing case, <sup>i</sup>2 missing cases, <sup>j</sup>4 missing cases
Table 4.2

*Descriptions and Examples of Inaccurate and Accurate Episodic Details of the Staged Event*

<table>
<thead>
<tr>
<th>Category</th>
<th>Description</th>
<th>Examples from Staged Event</th>
</tr>
</thead>
<tbody>
<tr>
<td>a) Inaccurate Episodic Detail Subcategories and Types of Memory Errors</td>
<td></td>
<td></td>
</tr>
<tr>
<td>i) Event - Approximation</td>
<td>An imprecise event detail</td>
<td>“You had <em>cheese</em> pizza for lunch” (instead of <em>pepperoni</em>)</td>
</tr>
<tr>
<td>Confabulation</td>
<td>A completely false event detail</td>
<td>“It was <em>raining</em> outside” (incorrect – sunny)</td>
</tr>
<tr>
<td>ii) Place - Approximation</td>
<td>An imprecise place detail</td>
<td>“We started on the 5<em>th</em> floor” (instead of 6<em>th</em> floor)</td>
</tr>
<tr>
<td>Confabulation</td>
<td>A completely false place detail</td>
<td>“I ate lunch in the <em>cafeteria</em>” (incorrect – lunch room)</td>
</tr>
<tr>
<td>iii) Time - Approximation</td>
<td>An imprecise time detail</td>
<td>“It was on August 15<em>th</em>” (instead of the 16<em>th</em>)</td>
</tr>
<tr>
<td>Confabulation</td>
<td>A completely false time detail</td>
<td>“The lunch started at 3<em>pm</em>” (incorrect – 12pm)</td>
</tr>
<tr>
<td>ii) Perceptual - Approximation</td>
<td>An imprecise perceptual detail</td>
<td>“You wore a <em>purple</em> sweater” (instead of <em>pink</em>)</td>
</tr>
<tr>
<td>Confabulation</td>
<td>A completely false perceptual detail</td>
<td>“I saw <em>needles</em> in the display” (incorrect - <em>coins</em>)</td>
</tr>
</tbody>
</table>

b) Accurate Episodic Detail Subcategories

<table>
<thead>
<tr>
<th>Category</th>
<th>Description</th>
<th>Examples from Staged Event</th>
</tr>
</thead>
<tbody>
<tr>
<td>i) Event</td>
<td>Accurate description of happenings, actions, people involved, clothing, and the weather</td>
<td>“I <em>counted the footprints</em>”</td>
</tr>
<tr>
<td>ii) Place</td>
<td>Accurate descriptions of the location (i.e., province, city, street, building, room, part of room)</td>
<td>“We started on the 6<em>th</em> floor”</td>
</tr>
<tr>
<td>iii) Time</td>
<td>Accurate descriptions of the year, season, month, date, day of week, and time of day</td>
<td>“It was in <em>January</em>”</td>
</tr>
<tr>
<td>iv) Perceptual</td>
<td>Accurate descriptions of sensory and visual details, body position, orientation in space, duration of event</td>
<td>“I was sitting on the <em>right side</em> of the table”</td>
</tr>
</tbody>
</table>
Table 4.3

*Frequency Scores, Group Means, and Standard Deviations (in Parentheses) for Demographic Measures and Hippocampal Volumes*

<table>
<thead>
<tr>
<th></th>
<th>Controls (N = 26)</th>
<th>CH (N = 26)(^a)</th>
<th>HYPO (N = 16)(^b)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Learning Disability</td>
<td>0</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Diagnosis of ADHD</td>
<td>0</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Sex (number of males)</td>
<td>9</td>
<td>11</td>
<td>11</td>
</tr>
<tr>
<td>SES</td>
<td>52.35 (10.44)</td>
<td>48.12 (9.68)</td>
<td>50.29 (10.41)</td>
</tr>
<tr>
<td>Age</td>
<td>10.46 (0.95)</td>
<td>11.36 (1.41)</td>
<td>10.12 (0.49)</td>
</tr>
<tr>
<td>WASI IQ score</td>
<td>118.04 (10.85)</td>
<td>104.12 (8.89)</td>
<td>112.94 (12.12)</td>
</tr>
<tr>
<td>Retention Interval (in years)</td>
<td>4.04 (2.05)</td>
<td>4.90 (2.24)</td>
<td>5.00 (2.93)</td>
</tr>
<tr>
<td>Intracranial volume (mm(^3))(^c)</td>
<td>1720.03 (146.80)</td>
<td>1688.50 (159.64)</td>
<td>1748.06 (188.30)</td>
</tr>
<tr>
<td>Total hippocampus (mm(^3))</td>
<td>3841.42 (454.46)</td>
<td>3829.81 (471.32)</td>
<td>3560.97 (508.78)</td>
</tr>
<tr>
<td>Right hippocampus (mm(^3))</td>
<td>1961.92 (247.85)</td>
<td>1947.64 (253.77)</td>
<td>1829.90 (267.53)</td>
</tr>
<tr>
<td>Right posterior (mm(^3))</td>
<td>1038.45 (151.52)</td>
<td>1029.05 (119.26)</td>
<td>953.82 (187.19)</td>
</tr>
<tr>
<td>Right anterior (mm(^3))</td>
<td>923.49 (135.60)</td>
<td>918.60 (215.72)</td>
<td>876.08 (165.37)</td>
</tr>
<tr>
<td>Left hippocampus (mm(^3))</td>
<td>1879.50 (223.31)</td>
<td>1882.16 (229.75)</td>
<td>1731.08 (246.97)</td>
</tr>
<tr>
<td>Left posterior (mm(^3))</td>
<td>1022.91 (135.60)</td>
<td>1025.95 (119.75)</td>
<td>965.49 (160.36)</td>
</tr>
<tr>
<td>Left anterior (mm(^3))</td>
<td>856.23 (169.26)</td>
<td>857.03 (231.69)</td>
<td>775.11 (167.55)</td>
</tr>
</tbody>
</table>

\(^a\) 3 CH did not complete sMRI scans; \(^b\) 1 HYPO did not complete the sMRI scan; \(^c\) Expressed per 1000 mm\(^3\)

Note: hippocampal volumes reflect group means after controlling for age, sex, and intracranial volume.
Figure 4.1

*Group Means for Proportion Accuracy Scores (a) and the Number of Total Inaccurate and Total Accurate Details Recalled (b) in the Recall + Specific Probe Condition*

(a)

[Proportion Accuracy Score Chart]

(b)

[Number of Details Recalled Chart]

Error bars indicate standard error of the mean
Figure 4.2

*Group Means for the Number of Details Recalled from Each Inaccurate Episodic Detail Subcategory (a) and Each Accurate Episodic Detail Subcategory (b) in the Recall + Specific Probe Condition*

(a) 

**Recall + Specific Probe**

Error bars indicate standard error

(b) 

**Recall + Specific Probe**

Error bars indicate standard error
Figure 4.3

Scatterplots of Total Hippocampal Volumes by Proportion Accuracy Scores from the Staged Event for Controls (a), HYPO (b), and CH (c)

a) CON

\[ y = 8 \times 10^{-6} x + 0.8117 \]

\[ R^2 = 0.0038, \quad p = .782 \]

b) HYPO

\[ y = 6 \times 10^{-5} x + 0.6026 \]

\[ R^2 = 0.2434, \quad p = .057 \]

c) CH

\[ y = 8 \times 10^{-5} x + 0.5103 \]

\[ R^2 = 0.2099; \quad p = .060 \]
Figure 4.4

Scatterplots of Early Thyroid Stimulating Hormone (TSH) Values by Proportion Accuracy Scores from the Staged Event for HYPO (a) and CH (b)

Note: each graph depicts raw values before accounting for covariates
Chapter 5
Study IV: Hippocampal Activation during Episodic and Semantic Autobiographical Memory Retrieval in Typically Developing Children and Children with Early Thyroid Hormone Deficiency

5.1 Introduction

Autobiographical memory (AM) retrieval consists of both an episodic component, which involves retrieving details about specific past events, and a semantic component, which involves retrieving personal facts (Levine et al., 2002). Recent neuroimaging studies have shown that both episodic and semantic AM retrieval activate a common network of brain regions that includes the hippocampus and parahippocampal gyrus (PHG; see Figure 1.7 and Svoboda et al., 2006 for a review). However, studies directly contrasting episodic and semantic AM retrieval in adults have shown greater activity within the hippocampus and PHG, as well as increased interconnectivity between the hippocampus and PHG, during episodic AM retrieval than during semantic AM retrieval (Hoscheidt et al., 2001; Maguire & Mummery, 1999; Maguire, Mummery, & Büchel, 2000; Ryan et al., 2001; Svoboda & Levine, 2009). Similarly, lesion studies have shown that patients with hippocampal damage exhibit deficits in episodic AM, but not semantic AM, indicating that episodic AM is more critically dependent on the hippocampus than semantic AM (Addis et al., 2007; Maguire et al., 2001; St-Laurent et al., 2009; Viskontas et al., 2000).

The hippocampus is a critical structure for episodic AM retrieval because it reintegrates contextual and visuospatial details from past events, thus allowing for greater re-experiencing and visualization of past event at the time of recollection (Eldridge et al., 2000; Gilboa et al., 2004). The PHG, which is critically involved in visual imagery and spatial processing (Bohbot et al., 1998; Ganis, Thompson, & Kosslyn, 2004), also plays an important role in episodic AM retrieval for two reasons. First, the posterior PHG is involved in the retrieval of visuospatial details because it acts as a key relay zone between the posterior hippocampus and neocortical
association areas involved visuospatial processing (e.g., posterior cingulate and retrosplenial cortex; Powell et al., 2004; Suzuki & Amaral, 1994). Second, the anterior PHG, which includes the entorhinal cortex, acts as a major communication zone between the anterior hippocampus and the medial prefrontal cortex, which is critically involved in self-referential processing and episodic AM retrieval (Cabeza et al., 2004; Insauti, Herrero, & Witter, 1997; Kahn, Andrews-Hanna, Vincent, Snyder, & Buckner, 2008; Valenti & Grace, 2009). Thus, both the hippocampus and PHG are essential brain structures for episodic AM retrieval.

Surprisingly, despite an extensive literature examining brain activity during episodic and semantic AM retrieval in adults, comparable studies examining brain activity during AM retrieval have not yet been conducted in children. Previous behavioural studies have shown that episodic AM develops gradually across childhood (Picard et al., 2009; Piolino et al., 2007), while findings from structural neuroimaging studies indicate that the hippocampus continues to increase in size during childhood (i.e., mainly in the posterior hippocampus and dentate gyrus; Gogtay et al., 2006) and does not reach adult levels of synaptic connectivity until late adolescence (Benes et al., 1994; Giedd et al., 1996; Grieve et al., 2011; Huttenlocher & Dabholkar, 1997; Suzuki et al., 2005). Given these significant changes during development, it is unclear whether children exhibit similar patterns of activation within the hippocampus during episodic AM retrieval as adults or whether their patterns of hippocampal activation differ due to immature functioning of the hippocampus and AM neural network. Furthermore, no study has yet examined hippocampal activation during episodic and semantic AM retrieval in children with hippocampal abnormalities and episodic AM impairments, despite numerous comparable studies in adult patients with hippocampal damage.

One piece of evidence suggesting that early hippocampal damage may alter hippocampal activity during episodic AM retrieval in children is the work of Maguire and colleagues on patient Jon, who sustained extensive bilateral damage to the hippocampus, but not the PHG, at
birth and showed significant deficits in episodic memory (Maguire et al., 2001). Using fMRI, Maguire et al. (2001) showed that during episodic AM retrieval, patient Jon exhibited bilateral activation of the hippocampus rather than the left-lateralized pattern observed in healthy young adults. Moreover, he showed abnormal connectivity between his hippocampus and PHG during episodic AM retrieval (Maguire et al., 2001). According to Maguire et al. (2001), Jon’s atypical pattern of neural activity may reflect functional reorganization and compensation following his early hippocampal damage. Similarly, Addis et al. (2007) reported that patients with temporal lobe epilepsy, who often experience hippocampal damage later in life, exhibit reductions in hippocampal activation and altered connectivity between the hippocampus and parahippocampal gyrus, which may also reflect functional reorganization of neural circuits involved in episodic AM retrieval. Given these findings, it is possible that children with abnormal hippocampal development could exhibit abnormal hippocampal activation during episodic AM retrieval relative to typically developing children; however, this hypothesis has not yet been tested.

Thus, the primary purpose of the present study was to investigate hippocampal activation during episodic and semantic AM retrieval in typically developing children and children who experienced early thyroid hormone (TH) deficiency using functional MRI (see section 5.2.9 for a detailed description of functional MRI). Our sample of children with early TH deficiency included offspring of women with treated hypothyroidism during pregnancy (HYPO) and children with early-treated congenital hypothyroidism (CH). These children were exposed to abnormally low levels of TH either throughout gestation (i.e., HYPO), or during late gestation and the first few weeks of life until treatment was provided (i.e., CH). Notably, children with early TH deficiency exhibit weaknesses in episodic AM recall and accuracy (see Studies II and III), as well as reduced hippocampal volumes (see Study II for HYPO and Wheeler et al., 2011, for CH), relative to controls. In addition, animal models of CH and HYPO have also shown that both CH and HYPO conditions are associated with abnormal synaptic functioning within
hippocampal neural circuits (Gilbert & Paczkowski, 2003; Liu et al., 2010; Madeira et al., 1992), which could lead to abnormal hippocampal functioning during episodic AM retrieval.

In order to examine hippocampal function during episodic and semantic AM retrieval, we created a modified version of the sentence verification task used extensively by Maguire and colleagues (e.g., Maguire & Frith, 2003; Maguire & Mummery, 1999; Maguire et al., 2000; 2001). This fMRI task, which requires participants to differentiate true from false statements or questions, enables researchers to compare hippocampal activation across three separate conditions of memory retrieval. The three conditions are: (a) personal episodic, involving the retrieval of autobiographical events; (b) personal semantic, involving the retrieval of autobiographical facts; and (c) general semantic, involving the retrieval of general information. Maguire and colleagues have used this task to demonstrate robust hippocampal activation during episodic AM retrieval (i.e., the PE condition) in healthy young adults, older adults, and patient Jon (e.g., Maguire & Frith, 2003; Maguire et al., 2000; 2001). In addition, this task is particularly useful for investigating AM retrieval in pediatric populations who may have difficulty performing lengthy or complex tasks during MRI scanning because: (a) trials can be short because the stimuli identify specific event details (i.e., reducing the need for lengthy memory search and retrieval operations) and short trials are more likely to sustain children’s attention, and (b) accuracy scores can be obtained to determine if participants were able to adequately perform the task. Importantly, Maguire et al. (2001) showed that patient Jon was able to perform this task at a comparable level as controls. For example, his accuracy score (>88% correct), which was based on parental verification of the original event details, was similar to the accuracy scores observed in controls (Maguire et al., 2001). This finding indicates that significant group differences in patterns of brain activation between patient Jon and controls were not due to differences in task performance, but rather due to possible alterations in neural connectivity or the use of different cognitive strategies (Maguire et al., 2001).
The first aim of the present study was to examine whether greater hippocampal activation was evident during episodic AM retrieval than during semantic AM retrieval in both typically and atypically developing children between 9 and 11 years of age. Given that no study has previously used fMRI to examine AM retrieval in children, it was difficult to predict whether our findings would replicate those found previously in adults or whether different patterns of hippocampal activation would be observed due to immaturity within the AM neural network. However, because several studies have shown that the hippocampus is preferentially active during episodic AM retrieval in several different populations, including young adults, older adults, and a young adult with hippocampal damage (Maguire & Firth, 2003; Maguire et al., 2000; 2001), it was hypothesized that children with early TH deficiency and typically developing controls would show a similar pattern of greater hippocampal activation during episodic AM retrieval than during semantic AM retrieval. Our second aim was to investigate whether children with early TH deficiency exhibit abnormal hippocampal activation during episodic AM retrieval relative to typically developing children. Based on Maguire et al.’s (2001) case study of patient Jon who exhibited bilateral hippocampal activation during episodic AM retrieval, it was hypothesized that children with early TH deficiency may show greater bilateral hippocampal activation during episodic AM retrieval, but not during semantic AM retrieval, than controls.

5.2 Methods

5.2.1 Participants

Forty-five children (56% male) between 9 and 11 years of age \((M = 9.93; SD = 0.39)\) were recruited for the present study. The sample included 7 CH, 19 HYPO, and 19 typically developing controls. All participants had previously participated in Study II. The exclusionary criteria were identical to Study II; however, additional exclusionary criteria for the present study included left-handedness and the presence of braces or permanent metal implants. Four HYPO participants were excluded, one for left-handedness and three because their mothers’ TSH values
were within a normal range throughout pregnancy. Thus, the remaining sample consisted of 41 right-handed children (54% male) between 9 and 11 years of age ($M = 9.93$, $SD = 0.41$) and included 7 CH, 15 HYPO, and 19 controls. In the CH group, four children had athyrosis (i.e., an absent or dysfunctional thyroid gland), two had ectopic or lingual glands (i.e., an abnormally located gland), and one had dyshormonogenesis (i.e., a defect in TH synthesis). All CH participants had elevated thyroid stimulating hormone (TSH) levels at birth and fulfilled diagnostic criteria for CH (see Table 5.1 for early TSH values in CH). All mothers of children in the HYPO group had elevated TSH levels during at least the first half of pregnancy and all were treated with synthetic TH during pregnancy (see Table 5.1 for their TSH values).

5.2.2 General Procedure

All parents or guardians provided written consent for participation in this study while participants also provided verbal assent. Participants were tested individually over three separate days in the Psychology Department at SickKids. On Day 1, participants took part in a neuropsychological assessment of their intelligence and general memory ability (assessed in Study II) and a staged event (assessed in Study III), while parents completed several questionnaires. On Day 2, approximately four and a half months after Day 1 ($M = 4.80$; $SD = 2.42$), participants completed a pre-scan interview, consisting of a Personal Semantic Questionnaire and the Children’s Autobiographical Interview (CAI). One examiner (K.W.) conducted all of the pre-scan interviews. Immediately after the pre-scan interview, participants underwent structural MRI scanning in a 1.5 Tesla Signa GE scanner at the SickKids Diagnostic Imaging Unit. A neuroradiologist examined all structural MRI images for neuroradiological abnormalities and sent written reports to participants’ family physicians.

Approximately one year after Day 1 ($M = 12.24$; $SD = 4.60$), participants returned to SickKids for Day 3 and completed the 25-minute fMRI task. Immediately prior to scanning, all
participants underwent pretraining of the fMRI task. After scanning, participants indicated how well they were able to visualize each event while in the scanner using a 7-point scale \((1 = I couldn’t see it at all, 7 = really clear like I was seeing it in front of me)\). At the end of Day 3, participants were given two movie certificates and parents were compensated for transportation. All procedures were approved by the Research Ethics Board of SickKids and the Office of Research Ethics at the University of Toronto.

5.2.3 Demographic Information and Assessment of Intelligence

Demographic information was obtained from all parents using the same demographic questionnaire from Study I. Intelligence was evaluated using the Vocabulary and Matrix Reasoning subtests of the Wechsler Abbreviated Scale of Intelligence (WASI; Wechsler, 1999), which yields an estimate of Full Scale IQ.

5.2.4 Early TSH Levels and TH Treatment Values for CH and HYPO

For CH participants, information was obtained on early TSH and TH treatment values from medical health records at SickKids (see Table 5.1 for missing cases). For HYPO participants, maternal TSH and TH treatment values during pregnancy were obtained from the participants’ family physicians (see Table 5.1 for missing cases).

5.2.5 Pre-scan Interview

The pre-scan interview consisted of a Personal Semantic Questionnaire, which was developed for the present study in order to collect personal semantic information for the fMRI task (see Appendix N for the Personal Semantic Questionnaire), as well as the same Children’s Autobiographical Interview (CAI) from Study I (see Study I for a more detailed description of the CAI). Unlike in Study I, however, participants in this study were asked to recall four naturally occurring autobiographical events that had occurred within the last three years and not
within the last month from a provided list of sample AMs (see Appendix C for sample AMs), as well as the staged event, in order to collect enough episodic AM data for the fMRI task (Note: nine participants did not complete the staged event and therefore recalled five naturally occurring autobiographical events). In addition, participants were also asked to generate short titles for each AM that served as retrieval cues during pretraining and the fMRI task. All interviews were transcribed and double-checked for transcription errors by K.W.

5.2.6 Structural MRI Acquisition, Processing, and Hippocampal Volumes

The hippocampal volume measurements collected in Study II were also used in the present study (see Study II for a more detailed description of structural image acquisition and processing, and manual tracing procedures). For the present study, inter-rater reliability was assessed for 56% of right and left hippocampal volumes selected at random within each group (5 CH, 8 HYPO, 10 CON). An intra-class correlation analysis using a one-way random effects model (McGraw & Wong, 1996) indicated coefficients of 0.75 (Cronbach $\alpha = 0.88$) for the right hippocampus and 0.80 (Cronbach $\alpha = 0.92$) for the left hippocampus.

5.2.7 Functional MRI Task

The functional MRI task consisted of a modified version of the sentence verification task used extensively by Maguire and colleagues (Maguire & Frith, 2003; Maguire & Mummery, 1999; Maguire et al., 2000; 2001). As shown in Appendix O, this task required participants to respond to yes or no questions from three separate conditions. The first condition was Personal Episodic (PE), which assessed episodic AM retrieval and consisted of 64 questions based on each participant’s CAI data collected during the pre-scan interview (e.g., Did you invite five friends to your birthday party?). Although PE questions were specifically tailored to each participant’s AMs, all efforts were made to ensure consistency in the categories of questions presented across participants (e.g., 50% event questions, 20% perceptual questions, etc.). In the PE condition,
false questions were created by making obvious adjustments to genuine AM details (e.g., ‘Was your party on a Friday?’ instead of ‘Was your party on a Saturday?’). The second condition, *Personal Semantic* (PS), assessed semantic AM retrieval and also served as a control for self-referential processing (i.e., thinking about personal information) and semantic retrieval. The PS condition included 96 questions generated from each participant’s data from the Personal Semantic Questionnaire (e.g., *Do you have two brothers?*). The third *General Semantic* (GS) condition served as a control for language processing and general memory retrieval. The GS condition consisted of 96 questions (see Appendix P for a list of the GS questions), which were adapted from a list of 270 general knowledge questions provided by P.V. Rekkas from Rekkas and Constable’s (2005) study (e.g., *Is Halloween in March?*). To sustain participants’ attention during the fMRI task, 25% of the questions across all three conditions were false (i.e., requiring a no response).

5.2.8 *Pretraining and Functional MRI Scanning*

Immediately prior to scanning, all participants underwent pretraining, which consisted of a complete practice run of the fMRI task using one of the five AMs recalled on Day 2 (i.e., the least detailed AM). The examiner (K.W.) provided instructions for the fMRI task (see Appendix Q for instructions), as well as the AM titles that participants produced in their pre-scan interview, to avoid confusion and ensure that participants would be able to recall each event during scanning. In order to encourage greater retrieval during the PE condition, participants were told to try their best to visualize and re-experience the past event to the best of their ability while responding to each question. The pretraining task was presented using a laptop computer system and participants responded using a MR-compatible response box.

During scanning, questions from the fMRI task were presented visually in black text on a white background using a laptop computer system connected to Avotec fiber-optic MR-
compatible goggles. Superlab 4.5 software (Cedrus Corporation) was used for the presentation and timing of all stimuli. Participants responded with the same MR-compatible response box used during pretraining and the designated response buttons (e.g., button 1/pointer finger = yes, button 2/middle finger = no) were randomly assigned and counterbalanced across participants. The scanning session consisted of a structural scan (i.e., to acquire anatomical images for localization of functional activity and coregistration) and four functional runs, each corresponding to a different AM and lasting 6.13 minutes. The position of the structural scan (i.e., before or after the fMRI task) was counterbalanced across participants. Before each functional run, participants were presented with a 20-second ‘instruction’ screen, which provided the AM title corresponding to the upcoming run and a reminder of the response button allocation (e.g., ‘respond YES with your pointer finger and NO with your middle finger’). Each functional run included four PE, four PS, and four GS blocks, each separated by a 4-second fixation period and a 1-second visual cue of the upcoming block (see Appendix O for the experimental design). All blocks were 24 seconds in length and were counterbalanced across each run. For each PE block, four questions were presented, each for 6 seconds, and participants were required to respond before the 6 seconds had elapsed. Within each of the PS and GS blocks there were six questions that were each presented for 4 seconds. These time scales were chosen based on pilot data indicating there was sufficient time for memory retrieval and for providing a response. The positions of false questions were randomized within each block.

5.2.9 Functional MRI Data Acquisition and Processing

Functional MRI measures changes in blood flow (i.e., the hemodynamic response) and more specifically, changes in the ratio of oxyhemoglobin to deoxyhemoglobin within the blood (i.e., the blood oxygen level dependent BOLD response) that are related to increased neural activity within the brain during specific tasks (Amaro & Barker, 2006). During fMRI scanning, brain
regions with increased task-related neural activity, increased blood flow, and a high concentration of oxyhemoglobin will be associated with high BOLD signal intensity (i.e., a brighter image; Amaro & Barker, 2006). In the present study, functional images were collected using a GE Signa 1.5 Tesla MR research scanner with an 8-channel head coil. To acquire anatomical images for localization of functional activity and coregistration with functional images, a standard 3-D fast spoiled gradient-echo (FSPGR) T1-weighted MRI sequence in the axial plane was obtained (TR = 10.37ms; TE = 4.26ms; TI = 300ms; flip angle = 20 degrees; FOV = 240mm; Acquisition Matrix = 256 x 192; Slice thickness = 2mm, no gap). Functional images were acquired with gradient echo type echo planar imaging (EPI-GRE) T2* weighted pulse sequences (TR = 2000ms; TE = 40 ms, flip angle = 90°, FOV = 240mm, Matrix = 64 x 64). Twenty-five slices (5mm thick, 1mm gap) were acquired in a coronal-oblique orientation, perpendicular to the long axis of the hippocampus in order to minimize partial voluming effects of the hippocampus. Behavioural data from each participant (i.e., accuracy scores and reaction times) were recorded using Superlab 4.5 software.

Functional imaging data were processed using SPM5 software (Statistical Parametric Mapping 5; Wellcome Department of Imaging Neuroscience). The first three functional frames were discarded to allow for signal equilibrium. The pre-processing stream involved extracting brain volumes from the skull and cerebral spinal fluid according to established criteria and automated algorithms. Functional images were realigned for motion correction, co-registered to the participant’s T1-weighted structural image, spatially normalized to the Montreal Neurological Institute EPI template, resampled at a voxel size of 4 x 4 x 4 mm, and smoothed spatially with a 8 mm full-width half-maximum Gaussian filter to accommodate inter-subject anatomical variability. Because the average activation across an entire block was used in group comparisons, no correction was made for slice timing effects. Functional images were assessed
for excessive motion (i.e., $> \pm 1$ mm and/or $\pm 1$ degree rotation from baseline) and any individual blocks containing large motion spikes were removed from the analysis.

### 5.2.10 Functional MRI Data Analysis

Data were analyzed using SPM5 according to the three conditions: Personal Episodic (PE), Personal Semantic (PS), and General Semantic (GS). The main contrasts of interest were: (a) PE > GS, which assessed whether greater hippocampal activity was evident during episodic AM retrieval than general semantic memory retrieval; (b) PE > PS, which assessed whether greater hippocampal activity was evident during episodic AM retrieval than semantic AM retrieval; (c) PS > GS, which assessed whether greater hippocampal activity was evident during semantic AM retrieval than general semantic memory retrieval; and (d) PS > PE, which assessed whether greater hippocampal activity was evident during semantic AM retrieval than episodic AM retrieval.

First-level analyses of individual participants’ data were processed using a fixed-effects model to examine differences in hippocampal activation (i.e., measured by the BOLD response) across the three conditions. Data from each contrast were then entered into a second-level random effects t-test to assess group differences in hippocampal activation. Given that the primary focus of the present study was to assess activation with the hippocampus during episodic and semantic AM retrieval, a hypothesis-driven region of interest (ROI) analysis of the hippocampal complex, which included the hippocampus and parahippocampal gyrus, was used. For the ROI analysis, we applied a ROI mask created in MNI space using MARINA (Bertram Walter Bender Institute of Neuroimaging, University of Giessen) and used the Small Volume Correction (SVC) option in SPM5. For these analyses, an overall significance threshold of $p < .05$ with a False Discovery Rate (FDR) correction and a minimum of five contiguously active voxels was used. Total hippocampal volumes and accuracy scores from the PE condition were
entered as covariates in order to remove the effects of individual variation in these variables from the results.

Finally, multiple regressions were conducted in SPM5 in order to identify possible predictors of hippocampal activation during episodic AM retrieval in children with early TH deficiency and typically developing controls. Because we observed a similar pattern of results for the regression analyses across the PE > GS and PE > PS contrasts, only results from the PE > GS contrast are reported for brevity. The following four predictors were examined for the PE > GS contrast: (a) total hippocampal volume, after controlling for PE accuracy scores; (b) PE accuracy scores, after controlling for total hippocampal volume; (c) participants’ visualization ratings, after controlling for total hippocampal volume and PE accuracy scores; and (d) severity of early TH deficiency (i.e., TSH values) in CH and HYPO, after controlling for total hippocampal volume and PE accuracy scores. Only maternal TSH values from the first trimester (for HYPO) and newborn TSH values (for CH) were used as predictors because these variables reflected the period of greatest TH deficiency and for the HYPO group, contained the fewest number of missing cases. Given the exploratory nature of these regression analyses and the small size of the hippocampal ROI, an uncorrected significance threshold of $p < .10$ with small volume correction (SVC; $p < .05$) and a minimum of five contiguously active voxels was employed for these regression analyses.

5.2.11 Behavioural, Hippocampal Volume, and Early TSH Data Analysis

All behavioural, hippocampal volume, and TSH data were examined for outliers (i.e., > 3 SD from the mean). The only outlier found was for one HYPO participant who had low accuracy scores in the PS and GS conditions. Given our small sample sizes and the fact that PS and GS accuracy scores were not the main variables of interest and were not used as covariates, no correction was made for this outlier. All variables of interest were examined for deviations in
skewness and kurtosis in order to assess the assumption of normality. The only variable to exceed the cutoffs for skewness (±2) and kurtosis (±2) was maternal TSH values in the first trimester and this variable was corrected using log10 transformation. Participants’ visualization ratings for all four AMs retrieved during the fMRI task were averaged together to create a total visualization rating composite score. Chi-squared tests were used to compare groups on sex distribution and ANOVAs were used to compare groups on age (measured in years), SES, IQ scores, and the behavioural measures (i.e., accuracy scores, reaction times, and participants’ visualization ratings). Finally, group differences in total, right, and left hippocampal volumes were examined a mixed-factor ANCOVA, with side (right or left hippocampal volume) as the repeated measure, group as the between-subjects variable, and age, sex, and intracranial volume as the control variables.

5.3 Results

5.3.1 Demographic and Hippocampal Volumes Results

Demographic data for each group are presented in Table 5.2. One CH participant and two HYPO participants had ADHD. No significant group differences were found in sex distribution, SES, or age. The CH group, however, had lower IQ scores, $F(2,38) = 6.11; p = .005; \eta^2_p = .24$, than HYPO and controls. Total, left and right hippocampal volumes are also presented in Table 5.2. Although CH and HYPO groups had smaller hippocampal volumes than controls, no significant group differences were found.

5.3.2 Behavioural Results

Behavioural data from the fMRI task are shown in Table 5.3. No significant group differences were observed in accuracy scores or reaction times for the PE, PS, and GS conditions ($ps > .05$). In addition, no significant group difference was found for participants’ visualization ratings of how well they could visualize each event while they were in the scanner ($p = .912$).
5.3.3 *fMRI Results: Group Differences in Hippocampal Activation*

Preliminary analyses revealed no significant differences between CH and HYPO groups in hippocampal activation across all analysis. Given this finding and the fact that the sample size of the CH group was small (N = 7), both groups were collapsed into a single TH-deficient group (N = 22) in order to gain statistical power for group comparisons of fMRI data (Note: significant group differences were evident before the two TH-deficient groups were collapsed). Table 5.4 shows the significant peak activated voxels in the hippocampus for each of the planned contrasts.

5.3.3.1 *Episodic AM Retrieval: PE > GS Contrast*

The PE > GS contrast was first examined in order to determine whether the episodic AM retrieval condition was associated with greater hippocampal activation than the general semantic memory retrieval condition. Results indicated that both TH-deficient and control groups showed bilateral activation of the hippocampus and PHG during episodic AM retrieval (see Figure 5.1a & b for the BOLD response). Direct statistical comparison between TH-deficient and control groups indicated that during episodic AM retrieval, the TH-deficient group showed greater activity than controls in the left anterior hippocampus and PHG (see Figure 5.1c). In contrast, controls showed no areas of increased activity relative to the TH-deficient group during episodic AM retrieval.

5.3.3.2 *Episodic AM Retrieval: PE > PS Contrast*

The PE > PS contrast was analyzed to examine whether episodic AM retrieval activated the hippocampus to a greater extent than semantic AM retrieval (i.e., retrieval of personal semantic information). Results indicated that episodic AM retrieval uniquely activated bilateral regions of the hippocampus and PHG in the TH-deficient group (see Figure 5.2a). For controls, however, only the right posterior hippocampus and PHG were uniquely active during episodic AM retrieval (see Figure 5.2b). Direct statistical comparison of the two groups revealed that during
episodic AM retrieval, the TH-deficient group showed greater activity in bilateral regions of the hippocampus and PHG than controls (see Figure 5.2c). In contrast, controls showed no areas of increased activity relative to the TH-deficient group.

5.3.3.3 Semantic AM Retrieval: PS > GS Contrast

The PS > GS contrast was examined in order to determine whether greater hippocampal activation was evident during semantic AM retrieval than general semantic memory retrieval. Results indicated that both TH-deficient and control groups activated the left hippocampus and PHG during semantic AM retrieval (see Figure 5.3a & b). In addition, controls also activated the right hippocampus and PHG (see Figure 5.3b). Direct statistical comparison of the two groups revealed no significant differences in hippocampal activity for the PS > GS contrast, signifying that the groups were indistinguishable in terms of hippocampal activation during semantic AM retrieval.

5.3.3.4 Semantic AM Retrieval: PS > PE Contrast

The PS > PE contrast was analyzed to examine whether semantic AM retrieval activated the hippocampus or PHG to a greater extent than episodic AM retrieval. However, no significant activation in the hippocampus or PHG was found in the PS > PE contrast in either group.

5.3.4 fMRI Results: Predictors of Hippocampal Activation

Multiple regression analyses were used to assess the effects of certain predictor variables (i.e., total hippocampal volumes, PE accuracy scores, participants’ visualization ratings, and severity of early TH deficiency) on hippocampal activation during episodic AM retrieval (i.e., the PE > GS contrast). Table 5.5 shows the significant peak activated voxels in the hippocampus for each multiple regression analysis.

5.3.4.1 Effect of Total Hippocampal Volumes on Hippocampal Activation
Multiple regression analyses using total hippocampal volumes as the predictor variable indicated that for the TH-deficient group, smaller hippocampal volumes were associated with greater activity in the left hippocampus and PHG during episodic AM retrieval (see Figure 5.4a). In controls, however, larger hippocampal volumes were associated with greater activity in the left hippocampus and PHG during episodic AM retrieval (see Figure 5.4b).

5.3.4.2 Effect of PE Accuracy Scores on Hippocampal Activation

Results from the multiple regression analyses with PE accuracy scores as the predictor variable indicated that for both TH-deficient and control groups, higher PE accuracy scores (i.e., better episodic AM performance) predicted greater activity in the left hippocampus and PHG during episodic AM retrieval (see Figure 5.5a & b).

5.3.4.3 Effect of Participants’ Visualization Ratings on Hippocampal Activation

When participants’ visualization ratings were entered as the predictor variable, higher visualization ratings in the TH-deficient group were associated with greater bilateral activity in hippocampus and PHG during episodic AM retrieval (see Figure 5.6). No significant effect of visualization ratings on hippocampal activation was found in controls.

5.3.4.4 Effect of TH Deficiency Severity on Hippocampal Activation

Separate analyses in HYPO and CH were conducted using maternal TSH values during the first trimester for HYPO and TSH values at birth for CH as predictors of hippocampal activation during episodic AM retrieval. In both HYPO and CH, elevated TSH values (signifying greater TH deficiency) predicted greater activity in the left hippocampus and PHG during episodic AM retrieval (see Figure 5.7a & b). In addition, in the HYPO group, elevated maternal TSH values during the first trimester also predicted greater activity in the right hippocampus and PHG during episodic AM retrieval (see Figure 5.7a).
5.3 Discussion

The present study was the first to examine hippocampal activation during AM retrieval in both typically developing children and children with hippocampal abnormalities using fMRI. Our first aim was to investigate hippocampal activation during episodic and semantic AM retrieval in order to determine whether children between 9 and 11 years of age show similar or different patterns of hippocampal activation relative to those previously observed in adults (e.g., Maguire & Mummery, 1999). Although bilateral activation of the hippocampus and PHG was evident during both episodic and semantic AM retrieval (i.e., the PE > GS and PS > GS contrasts), TH-deficient and control groups both showed greater activity within the hippocampus and PHG during episodic AM retrieval (i.e., the PE > PS contrast) than during semantic AM retrieval (i.e., the PS > PE contrast). In particular, the TH-deficient group showed greater bilateral engagement of the hippocampus and PHG and controls showed greater recruitment of the right hippocampus and PHG when episodic AM retrieval was directly contrasted to semantic AM retrieval. These results are consistent with previous studies examining episodic and semantic AM retrieval in both younger and older adults who exhibited greater activation in the hippocampus and PHG during episodic AM retrieval than during semantic AM retrieval (Maguire & Frith, 2003; Maguire & Mummery, 1999). In addition, the regression analyses indicated that across both TH-deficient and control groups, higher PE accuracy scores (i.e., reflecting better episodic AM performance) were associated with greater activation within the anterior hippocampus and PHG during episodic AM retrieval. Several studies have shown that episodic AM retrieval activates the anterior hippocampus to a greater extent than the posterior hippocampus (Gilboa et al., 2004; Hoscheidt et al., 2010; Svoboda & Levine, 2009; Viard et al., 2007); however, further investigation into the functions of the anterior and posterior regions of the hippocampus is
required. Overall, our results appear to be consistent with the adult neuroimaging literature showing that the hippocampus and PHG are critical regions for episodic AM retrieval.

Our results also revealed that when using a sentence verification task, episodic AM retrieval is supported by a bilateral pattern of hippocampal activation in typically developing children (i.e., evident in the PE > GS contrast). In contrast, other studies that have used a similar sentence verification task have shown a more left-lateralized pattern of activation in healthy adults (Maguire & Mummery, 1999; Maguire et al., 2000). Interestingly, evidence indicates that as children age and acquire greater cognitive and processing abilities, there is a transition from immature bilateral patterns of cortical activation to more focal and lateralized patterns of activation, particularly around the ages of 12 to 14 (Martinez et al., 1997; Stiles, Moses, Passarotti, Dick, & Buxton, 2003). Given that all of the participants in the present study were under the age of 12, their bilateral recruitment of the hippocampus during episodic AM retrieval may be associated with immaturity within the AM neural network, as well as ongoing episodic AM development during late childhood (i.e., evident in Study I). Maguire and Frith (2003) recently showed that during episodic AM retrieval (i.e., both PE > GS and PE > PS contrasts), older adults exhibited greater activation of the right hippocampus and similar activation of the left hippocampus relative to healthy young adults using the sentence verification task. Based on these results, Maguire and Frith (2003) suggested that bilateral recruitment of the hippocampus in older adults may reflect neural compensation for normal age-related declines in episodic AM retrieval and processing within the AM neural network. Although age-related cognitive decline is not simply the reverse of cognitive development during childhood (Craik & Bialystok, 2006), the similar pattern of bilateral hippocampal activation during episodic AM retrieval in children and older adults using a sentence verification task suggests that both groups may exhibit some degree of neural compensation and altered connectivity within the AM neural network relative to young adults. However, given that these results are likely heavily dependent on the nature of the fMRI
AM paradigm employed (e.g., a sentence verification task), further investigation using different AM tasks is required to fully understand and compare brain activation patterns during episodic AM retrieval among children, young adults, and older adults.

The second aim of the present study was to examine how hippocampal activation during episodic AM retrieval in childhood is affected by early TH deficiency. The results indicated that children with early TH deficiency exhibited greater bilateral recruitment of the hippocampus and PHG than controls during episodic AM retrieval, but not during semantic AM retrieval. This finding corresponds with the behavioural results reported in Study II showing significant group differences between TH-deficient and control groups in episodic AM recall, but not semantic AM recall. In addition, our results are similar to those found by Maguire et al. (2001) in patient Jon who exhibited bilateral recruitment of the hippocampus during episodic AM retrieval, in contrast to controls, who exhibited a left-lateralized pattern of hippocampal activation. Finally, our results are also consistent with fMRI studies showing hyperactivation of the hippocampus and PHG during memory encoding in older individuals with mild cognitive impairment (i.e., a common precursor to dementia or Alzheimer’s disease), who exhibit reduced hippocampal volumes and episodic memory impairments relative to controls (Hämäläinen et al., 2006).

One possible explanation for why the TH-deficient group exhibited greater activation of the hippocampus and PHG than controls during episodic AM retrieval is that their hyperactivation could be a reflection of lasting perturbations in synaptic transmission, cell excitability, and neurotransmitter release that have been associated with early TH deficiency (Gilbert & Sui, 2006; Vara, Martínez, Santos, & Colino, 2002). For example, Vara et al. (2002) showed that rats who were rendered hypothyroid during the entire neonatal period exhibited enhanced neurotransmitter release within the hippocampus, which could influence electrical activity and the establishment of specific synaptic connections during development. In addition, early TH deficiency has been associated with alterations in the number and distribution of
dendritic spines within the hippocampus (Rami et al., 1986), and these structural alterations could lead to long-term functional changes in synaptic transmission and cell excitability (Sorra & Harris, 2000). Finally, Sui and Gilbert (2003) also showed that prenatal TH deficiency in rats can result in increased excitatory synaptic transmission (i.e., enhanced EPSP slope and population spike amplitude) within the CA1 field of the hippocampus, possibly due to abnormalities in neurotransmitter release or the inhibitory properties of hippocampal neurons.

Alternatively, our results in the TH-deficient group could represent a compensatory response in the context of poor hippocampal function given that: (a) hyperactivation of the hippocampus and PHG in the TH-deficient group was evident only during episodic AM retrieval, despite the fact that both episodic and semantic AM retrieval activated the hippocampus and PHG; and (b) no significant group differences were found in task performance (i.e., accuracy scores) or reaction times during episodic AM retrieval. In other words, children with early TH deficiency may require increased effort and greater bilateral activation of the hippocampus and PHG during episodic AM retrieval in order to reach the same level of retrieval success as controls. Interestingly, results from the regression analyses indicated that larger hippocampal volumes in controls predicted greater activation within the left hippocampus and PHG during episodic AM retrieval. In contrast, the TH-deficient group showed an opposite pattern with smaller total hippocampal volumes predicting greater activation within the left hippocampus and PHG during episodic AM retrieval. In addition, greater severity of TH deficiency in both CH and HYPO groups was found to predict greater activation in the hippocampus and PHG during episodic AM retrieval. Overall, converging evidence indicates that early TH deficiency and its adverse effects on the developing hippocampus are associated with greater bilateral activation of the hippocampus and PHG during episodic AM retrieval later in life.

Interestingly, hyperactivation during episodic AM retrieval in the TH-deficient group appeared to be most prominent in the left anterior PHG (i.e., the location of the most significant
peak voxel in the PE > GS and PE > PS contrasts). This region includes the entorhinal cortex, which has direct and extensive connections with the hippocampus and medial prefrontal cortex (Powell et al., 2004; Valenti & Grace, 2009) and supports both episodic AM recall and recollection-based recognition memory (Rosenbaum et al., 2008; Sauvage, Beer, Ekovich, Ho, & Eichenbaum, 2010). Given that our fMRI task is a measure of recollection-based recognition memory (Maguire et al., 2001), and the fact that the TH-deficient group showed normal performance on the fMRI task despite showing weaknesses in episodic AM recall in Study II, it is possible that the entorhinal cortex may have adopted a more prominent role than the hippocampus during episodic AM retrieval in the TH-deficient group, due to their abnormal hippocampal development. For example, Addis et al. (2007) found that patients with left temporal lobe epilepsy and significant left hippocampal damage showed an increased reliance on the left PHG and an altered neural network that bypassed the damaged hippocampal tissue during episodic AM retrieval. Alternatively, given that animal studies have shown that prenatal TH deficiency impairs the migration of neurons destined for the anterior hippocampus, causing them to end up in aberrant locations (Berbel et al., 2010; Lavado-Autric et al., 2003), it could also be possible these hippocampally-destined neurons ended up in the entorhinal cortex, due to its proximity to the anterior hippocampus, resulting in abnormal activation patterns within this region. Given the paucity of studies examining the effects of early TH deficiency on the PHG and entorhinal cortex, further investigation of these hypotheses is required in order to investigate whether early TH deficiency specifically alters structural and functional connectivity between the hippocampus and PHG.

Finally, our regression analyses also indicated that within the TH-deficient group, higher visualization ratings (i.e., a greater ability to visualize past events during scanning) predicted greater activity within the hippocampus and PHG during episodic AM retrieval, particularly within posterior regions of the hippocampus and PHG. This finding is supported by evidence
indicating that the posterior hippocampus and PHG are particularly involved in the retrieval of visuospatial details through direct connections with cortical regions that control visuospatial processing, such as the posterior cingulate and retrosplenial cortex (Hoscheidt et al., 2010; Khan et al., 2008; Suzuki & Amaral, 1994). Thus, similar to our results from Study III, visual imagery appears to play an important role in episodic AM retrieval.

It is important to note several limitations of the present study. First, both TH-deficient and control groups exhibited much more activation within the PHG than was expected. This finding may be due to the fact that our fMRI task measured recollection-based recognition memory, which may have a greater reliance on the PHG and entorhinal cortex than on the hippocampus when compared to tasks specifically measuring episodic AM recall (Addis et al., 2007; Ofen et al., 2007; Sauvage et al., 2010). However, Maguire et al. (2001) have argued that the sentence verification task reflects a mixture of both recognition and recall because the episodic AM details used in the task were originally elicited using a recall task and their participants report retrieving the original AMs when performing the task in the scanner. It is also possible that the specific location of hippocampal activation may be slightly distorted in our figures (i.e., appearing instead over the PHG) because we spatially normalized participants’ brain images to a standard adult brain template (i.e., the Montreal Neurological Institute EPI template), rather than a pediatric brain template. The process of spatially normalizing individual participants’ brain images to a standard brain template is necessary when conducting group comparisons in order to ensure all brain images are transformed into a common stereotactic space and to report the results using standardized coordinates (Kang, Burgund, Lugar, Petersen, & Schlaggar, 2003). Although there is some evidence that the use of adult templates for pediatric data may lead to distortion and misclassification of brain tissue due to differences in brain size and shape between children and adults (Poldrack, Pare-Bлагаev, & Grant, 2002; Wilke, Schmithorst, & Holland, 2003; Yoon, Fonov, Perusse, & Evans, 2009), other studies have
provided evidence that spatial normalization to an adult template is feasible in children older than 7 years of age (Kang et al., 2003; Muzik, Chugani, Juhasz, Shen, & Chugani, 2000). Given that our study is the first to examine hippocampal activation during episodic AM retrieval in typically developing children, our results should be interpreted with caution and future studies using pediatric brain templates are required in order to confirm our results.

Another limitation of the present study was that our task may not have provided participants with enough time to fully re-experience each AM during scanning, which could have lead to more superficial forms of episodic AM retrieval that are less reliant on the hippocampus (Levine et al., 2004; Rekkas & Constable, 2005). However, we assessed episodic AM retrieval using short recognition-based trials because our participants were children and it was important to sustain their attention during scanning, as well as measure their accuracy performance in order to ensure the TH-deficient and control groups performed at comparable levels. Finally, in order to identify possible predictors of hippocampal activation, a very liberal overall significance threshold ($p < .10$) was used for the regression analyses that may have increased the risk of making false-positive/Type I errors. The use of less stringent statistical criteria when investigating hippocampal activation is not uncommon given that the medial temporal lobe typically yields lower amplitude hemodynamic responses when compared to other brain regions (Hoscheidt et al., 2010). Due to the exploratory nature of these regression analyses, our results should be interpreted cautiously, especially our findings on the relation between TH deficiency severity and hippocampal activation in the CH group, considering the small sample size.

Taken together, the results of the present study provide critical new insight into hippocampal activation during episodic and semantic AM retrieval in typically developing children, as well as the effects of early TH deficiency on hippocampal function during episodic AM retrieval. Our results indicate that typically developing children show similar, albeit more bilateral, patterns of hippocampal activation during AM retrieval as those previously reported by
Maguire and colleagues in young adults. In addition, children with early TH deficiency exhibited greater bilateral recruitment of the hippocampus and PHG than controls during episodic AM retrieval, and the regression analyses revealed that greater severity of TH deficiency and greater reductions in hippocampal volumes in the TH-deficient group predicted hyperactivation of the hippocampus and PHG during episodic AM retrieval. Thus, early TH deficiency appears to have significant adverse effects on hippocampal structure and function, resulting in greater bilateral activation of medial temporal lobe structures during AM retrieval later in life. Additional fMRI research will be very helpful in determining whether individuals with early TH deficiency exhibit hyperactivation of the entire AM neural network or whether they also exhibit some regions of hypoactivation and altered effective connectivity within the AM neural network similar to patients with more severe hippocampal damage and episodic AM impairments, such as those with temporal lobe epilepsy (e.g., Addis et al., 2007) or Alzheimer’s disease (e.g., Sperling et al., 2010). Overall, the present study significantly contributes to the growing neuroimaging literature aimed at identifying the neural correlates of AM by providing novel data on hippocampal activation during AM retrieval in both typically and atypically developing children.
Table 5.1

*Group Means and Standard Deviations (in Parentheses) for Early Thyroid Stimulating Hormone (TSH) Values and Thyroid Hormone (TH) Treatment Values for CH and Mothers of HYPO*

<table>
<thead>
<tr>
<th></th>
<th>CH (N = 7)</th>
<th>HYPO (N = 15)</th>
</tr>
</thead>
<tbody>
<tr>
<td>TH treatment dose during pregnancy (mcg/day)&lt;sup&gt;a&lt;/sup&gt;</td>
<td>--</td>
<td>91.67 (29.32)</td>
</tr>
<tr>
<td>Trimester 1 TSH value (mU/L)&lt;sup&gt;b&lt;/sup&gt; (Normal range during pregnancy &lt; 2.5 mU/L)</td>
<td>--</td>
<td>8.85 (7.02)</td>
</tr>
<tr>
<td>Trimester 2 TSH value (mU/L)&lt;sup&gt;c&lt;/sup&gt;</td>
<td>--</td>
<td>8.04 (10.34)</td>
</tr>
<tr>
<td>Trimester 3 TSH value (mU/L)&lt;sup&gt;d&lt;/sup&gt;</td>
<td>--</td>
<td>3.68 (4.90)</td>
</tr>
<tr>
<td>Newborn TSH value (mU/L)&lt;sup&gt;e&lt;/sup&gt; (Normal range = 0.4-4.1 mU/L)</td>
<td>142.83 (100.24)</td>
<td>4.29 (3.11)</td>
</tr>
<tr>
<td>TSH value at diagnosis (mU/L)</td>
<td>122.43 (182.46)</td>
<td>--</td>
</tr>
<tr>
<td>T4 value at diagnosis (nmol/L)&lt;sup&gt;f&lt;/sup&gt; (Normal range = 50-150 nmol/L)</td>
<td>110.25 (114.20)</td>
<td>--</td>
</tr>
<tr>
<td>Age at diagnosis (in days)</td>
<td>17.29 (8.73)</td>
<td>--</td>
</tr>
<tr>
<td>Starting TH treatment dose (mcg/day)</td>
<td>41.14 (4.96)</td>
<td>--</td>
</tr>
<tr>
<td>Average childhood TSH value (mU/L)</td>
<td>8.56 (6.41)</td>
<td>--</td>
</tr>
</tbody>
</table>

Note: TSH = Thyroid Stimulating Hormone; higher TSH levels indicate more severe TH Deficiency; T4 = Throxine; <sup>a</sup> 3 missing cases, <sup>b</sup> 1 missing case; 93% of cases were elevated above 2.5 mU/L, <sup>c</sup> 3 missing cases; 83% of cases were elevated above 2.5 mU/L, <sup>d</sup> 4 missing cases; 55% of cases were elevated above 2.5 mU/L, <sup>e</sup> 1 missing CH cases and 4 missing HYPO cases (note: newborn TSH values for HYPO are from the newborn, not the mother), <sup>f</sup> 3 missing cases
Table 5.2

*Frequency Scores, Group Means, and Standard Deviations (in Parentheses) for Demographic Measures, Intracranial Volumes, and Hippocampal Volumes*

<table>
<thead>
<tr>
<th></th>
<th>Control (N=19)</th>
<th>CH (N = 7)</th>
<th>HYPO (N = 15)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Learning Disability</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Diagnosis of ADHD</td>
<td>0</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Sex (number of males)</td>
<td>9</td>
<td>3</td>
<td>10</td>
</tr>
<tr>
<td>SES</td>
<td>51.74 (11.54)</td>
<td>43.14 (11.22)</td>
<td>49.73 (11.03)</td>
</tr>
<tr>
<td>Age</td>
<td>9.84 (0.38)</td>
<td>10.00 (0.58)</td>
<td>10.00 (0.38)</td>
</tr>
<tr>
<td>WASI IQ score</td>
<td>116.74 (10.24)</td>
<td>103.29 (4.96)</td>
<td>115.53 (8.52)</td>
</tr>
<tr>
<td>Intracranial Volumes (mm$^3$)$^a$</td>
<td>1714.64 (171.51)</td>
<td>1708.69 (159.62)</td>
<td>1774.81 (146.72)</td>
</tr>
<tr>
<td>Total hippocampus (mm$^3$)</td>
<td>3747.90 (418.72)</td>
<td>3558.72 (493.48)</td>
<td>3577.30 (509.96)</td>
</tr>
<tr>
<td>Right hippocampus (mm$^3$)</td>
<td>1907.46 (211.73)</td>
<td>1804.47 (257.27)</td>
<td>1843.36 (270.48)</td>
</tr>
<tr>
<td>Left hippocampus (mm$^3$)</td>
<td>1840.43 (217.45)</td>
<td>1754.25 (249.28)</td>
<td>1733.94 (243.85)</td>
</tr>
</tbody>
</table>

$^a$Expressed per 1000 mm$^3$ Note: hippocampal volumes reflect group means after controlling for age, sex, and intracranial volume.
Table 5.3

*Group Means and Standard Deviations (in Parentheses) for fMRI Behavioural Data*

<table>
<thead>
<tr>
<th></th>
<th>Control (N=19)</th>
<th>CH (N = 7)</th>
<th>HYPO (N = 15)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PE Accuracy (%)</td>
<td>0.86 (0.06)</td>
<td>0.82 (0.08)</td>
<td>0.87 (0.06)</td>
</tr>
<tr>
<td>PS Accuracy (%)</td>
<td>0.93 (0.05)</td>
<td>0.90 (0.05)</td>
<td>0.92 (0.06)</td>
</tr>
<tr>
<td>GS Accuracy (%)</td>
<td>0.97 (0.04)</td>
<td>0.96 (0.06)</td>
<td>0.94 (0.10)</td>
</tr>
<tr>
<td>PE Reaction Time (ms)</td>
<td>3137.92 (675.25)</td>
<td>3284.68 (549.44)</td>
<td>3222.15 (545.66)</td>
</tr>
<tr>
<td>PS Reaction Time (ms)</td>
<td>2243.53 (438.26)</td>
<td>2438.11 (586.73)</td>
<td>2281.68 (373.68)</td>
</tr>
<tr>
<td>GS Reaction Time (ms)</td>
<td>2299.52 (476.85)</td>
<td>2472.85 (487.81)</td>
<td>2348.73 (370.34)</td>
</tr>
<tr>
<td>Visualization Rating</td>
<td>5.18 (0.70)</td>
<td>5.29 (0.47)</td>
<td>5.18 (0.42)</td>
</tr>
</tbody>
</table>
Table 5.4

*Significant Peak Activations in the Hippocampus Across Groups for Each Contrast (p < .05, FDR, SVC), After Controlling for Total Hippocampal Volumes and PE Accuracy Scores*

<table>
<thead>
<tr>
<th>Analyses Group</th>
<th>Side</th>
<th></th>
<th>Voxel-level</th>
<th>MNI Coordinates</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>p</td>
<td>FDR</td>
</tr>
<tr>
<td><strong>PE &gt; GS</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CON</td>
<td>L</td>
<td></td>
<td>0.000</td>
<td>5.23</td>
</tr>
<tr>
<td></td>
<td>R</td>
<td></td>
<td>0.001</td>
<td>4.31</td>
</tr>
<tr>
<td>TH</td>
<td>L</td>
<td></td>
<td>0.000</td>
<td>7.83</td>
</tr>
<tr>
<td></td>
<td>R</td>
<td></td>
<td>0.000</td>
<td>7.58</td>
</tr>
<tr>
<td>TH &gt; CON</td>
<td>L</td>
<td></td>
<td>0.010</td>
<td>3.31</td>
</tr>
<tr>
<td><strong>PE &gt; PS</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CON</td>
<td>R</td>
<td></td>
<td>0.000</td>
<td>5.37</td>
</tr>
<tr>
<td>TH</td>
<td>L</td>
<td></td>
<td>0.002</td>
<td>3.90</td>
</tr>
<tr>
<td></td>
<td>R</td>
<td></td>
<td>0.001</td>
<td>4.34</td>
</tr>
<tr>
<td>TH &gt; CON</td>
<td>L</td>
<td></td>
<td>0.008</td>
<td>3.27</td>
</tr>
<tr>
<td></td>
<td>R</td>
<td></td>
<td>0.023</td>
<td>2.79</td>
</tr>
<tr>
<td><strong>PS &gt; GS</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CON</td>
<td>L</td>
<td></td>
<td>0.000</td>
<td>4.62</td>
</tr>
<tr>
<td></td>
<td>R</td>
<td></td>
<td>0.001</td>
<td>4.52</td>
</tr>
<tr>
<td>TH</td>
<td>L</td>
<td></td>
<td>0.007</td>
<td>3.20</td>
</tr>
<tr>
<td><strong>PS &gt; PE</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>no significant voxels</td>
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</tbody>
</table>
Table 5.5

Results of the Regression Analyses ($p < .10$, SVC) for the PE > GS Contrast

<table>
<thead>
<tr>
<th>Analyses</th>
<th>Predictor Group</th>
<th>Side</th>
<th>Correlation (pos. or neg.)</th>
<th>Voxel-level</th>
<th>MNI Coordinates</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>$p$-unc</td>
<td>T-score</td>
</tr>
<tr>
<td><strong>PE &gt; GS</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Total hippocampal volumes</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CON</td>
<td>L</td>
<td>positive</td>
<td>0.009</td>
<td>2.63</td>
<td>2.36</td>
</tr>
<tr>
<td>TH</td>
<td>L</td>
<td>negative</td>
<td>0.053</td>
<td>1.68</td>
<td>1.62</td>
</tr>
<tr>
<td><strong>PE accuracy scores</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CON</td>
<td>L</td>
<td>positive</td>
<td>0.036</td>
<td>1.92</td>
<td>1.80</td>
</tr>
<tr>
<td>TH</td>
<td>L</td>
<td>positive</td>
<td>0.033</td>
<td>1.94</td>
<td>1.83</td>
</tr>
<tr>
<td><strong>Visualization ratings</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TH</td>
<td>L</td>
<td>positive</td>
<td>0.048</td>
<td>1.75</td>
<td>1.67</td>
</tr>
<tr>
<td>R</td>
<td>positive</td>
<td>0.056</td>
<td>1.65</td>
<td>1.59</td>
<td>28</td>
</tr>
<tr>
<td><strong>Severity of TH deficiency (TSH)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CH</td>
<td>L</td>
<td>positive</td>
<td>0.028</td>
<td>3.98</td>
<td>1.90</td>
</tr>
<tr>
<td>HYPO</td>
<td>L</td>
<td>positive</td>
<td>0.002</td>
<td>3.63</td>
<td>2.83</td>
</tr>
<tr>
<td>R</td>
<td>positive</td>
<td>0.042</td>
<td>1.91</td>
<td>1.73</td>
<td>32</td>
</tr>
</tbody>
</table>
Figure 5.1

Direct Comparison of Episodic AM Retrieval and General Semantic Retrieval (PE > GS) in the TH-Deficient Group (a), Controls (b), and the TH-Deficient Group > Controls Comparison (c)

(Note: Colour scale reflects the voxel T-score values with red = lower T-score and white = higher T-scores)
Figure 5.2

Direct Comparison of Episodic AM Retrieval and Semantic AM Retrieval (PE > PS) in TH- TH-Deficient Group (a), Controls (b), and the TH-Deficient Group > Controls Comparison (c)

(Note: Colour scale reflects the voxel T-score values with red = lower T-score and white = higher T-scores)
Figure 5.3

Direct Comparison of Semantic AM Retrieval and General Semantic Retrieval (PS > GS) in the TH-Deficient Group (a) and Controls (b)

(Note: Colour scale reflects the voxel T-score values with red = lower T-score and white = higher T-scores)
Figure 5.4

Significant Medial Temporal Lobe Activity During Episodic AM Retrieval (i.e., the PE > GS Contrast) that was Negatively Correlated with Total Hippocampal Volumes in the TH-Deficient Group (a) and Positively Correlated with Total Hippocampal Volumes in Controls (b)

(Note: Colour scale reflects the voxel T-score values with red = lower T-score and white = higher T-scores)
Figure 5.5

Significant Medial Temporal Lobe Activity During Episodic AM Retrieval (i.e., the PE > GS Contrast) that was Positively Correlated with PE Accuracy Scores in the TH-Deficient Group (a) and Controls (b)

(Note: Colour scale reflects the voxel T-score values with red = lower T-score and white = higher T-scores)
Figure 5.6

*Significant Medial Temporal Lobe Activity During Episodic AM Retrieval (i.e., the PE > GS Contrast) that was Positively Correlated With Participants’ Visualization Ratings in the TH-Deficient Group*

(Note: Colour scale reflects the voxel T-score values with red = lower T-score and white = higher T-scores)
Figure 5.7

*Significant Medial Temporal Lobe Activity During Episodic AM Retrieval (i.e., the PE > GS Contrast) that was Positively Correlated With TH Deficiency Severity (i.e., Elevated TSH Levels) in HYPO (a) and CH (b)*

(Note: Colour scale reflects the voxel T-score values with red = lower T-score and white = higher T-scores)
Chapter 6
General Discussion

The main goal of this dissertation was to investigate the effects of early TH deficiency on children’s episodic and semantic AM performance, as well as hippocampal structure and function, using a combination of behavioural and neuroimaging techniques. The two clinical pediatric populations studied in this dissertation were offspring of women treated (albeit inadequately) for hypothyroidism during pregnancy (HYPO) and children with early-treated congenital hypothyroidism (CH). The major focus of this dissertation was the hippocampus because both lesion and neuroimaging studies have shown that this region is a critical structure in the AM neural network (Addis et al., 2007; Gilboa et al., 2004; Maguire et al., 2001; Svoboda et al., 2006). For example, the hippocampus binds and integrates contextual details available at the time of encoding into a memory trace that can be sustained over time, and reintegrates these details during the retrieval and re-experiencing of past events (Buckner & Wheeler, 2001; Eichenbaum, 2000; Eldridge et al., 2000; Nadel & Moscovitch, 1997). This dissertation also specifically targeted the hippocampus because animal models of early TH deficiency have shown that the developing hippocampus is particularly vulnerable to damage when TH levels are abnormally low (Madeira et al., 1992). For example, animal studies have indicated that prenatal TH deficiency impairs critical periods of neurogenesis within and neuronal migration into the hippocampus, and it also leads to abnormal synaptic function and memory impairments in rats (Ausó et al., 2004; Berbel et al., 2010; Gilbert & Paczowski, 2003). In this general discussion, I first summarize the key findings across the four studies conducted in order to address our main goal. Second, I provide an overview of the main limitations of this dissertation. Third, I outline the implications of the findings in this dissertation. Finally, I demonstrate how our findings set the stage for future research on the effects of early TH deficiency as well as on AM retrieval in typically developing children.
6.1 Summary of the Results

Study I investigated age-related differences in episodic and semantic AM recall performance in a large sample of typically developing children and adolescents between 8 and 16 years of age. Given the paucity of studies investigating both episodic and semantic AM across childhood and adolescence, the primary goal of this study was to collect normative data on episodic and semantic AM using the new Children’s Autobiographical Interview (CAI), which was developed for this study. Importantly, Study I was critical for validating the use of the CAI in children for our subsequent investigations of AM recall and accuracy performance in a clinical pediatric population. Results from the CAI indicated that both episodic and semantic AM improved across childhood and adolescence, but greater age-related differences were evident in episodic AM than in semantic AM. These findings replicated those found by Picard et al. (2009) who used alternate measures of episodic and semantic AM (i.e., the TEMPau task and a personal semantic questionnaire) in a younger sample of participants between 6 and 11 years of age. Importantly, our results were the first to show that episodic AM recall continues to improve throughout adolescence. In addition, Study I revealed that the ability to clearly visualize past events at the time of recollection significantly was associated with children’s episodic AM recall performance, particularly the retrieval of perceptual details, signifying the importance of visual imagery for episodic AM retrieval.

Study II investigated episodic and semantic AM recall performance and hippocampal morphology in 9 to 14 year-old children with early TH deficiency relative to typically developing controls. The sample included children of treated hypothyroid women (HYPO) and children with early-treated CH. Results from the CAI indicated that when compared to controls, CH and HYPO groups both exhibited weaknesses in episodic AM, but not semantic AM. This finding corresponds to the results of previous studies that have used the adult version of the CAI to demonstrate impairments in episodic AM, but not semantic AM, in adult patients with
hippocampal damage (e.g., Addis et al., 2007; Rosenbaum et al., 2008; 2011; Steinworth et al., 2005; St-Laurent et al., 2009). CH and HYPO participants also showed particular difficulty recalling event details (i.e., the main happenings) and visual details (i.e., colours, objects, etc.) from specific past events. Interestingly, our finding of poor retrieval of visual details in CH and HYPO groups is consistent with: (a) our results showing that CH participants had lower delayed visuospatial memory scores on the Rey-O than controls, and in the HYPO group, greater severity of TH deficiency predicted lower delayed visuospatial memory scores on the Rey-O; (b) previous studies showing that visuospatial impairments are consistently observed in both CH and HYPO groups (Man et al., 1991; Mirabella et al., 2005; Oerbeck et al., 2005; Rovet, 1999), and (c) St-Laurent et al.’s (2009) study showing reduced generation of visual-perceptual details during episodic AM recall in adult temporal lobe epilepsy patients with significant hippocampal atrophy. Although retrieval of visual information was not the specific focus of this dissertation, our results suggest that early TH deficiency may impair the ability to encode and/or retrieve visual information from past events, and this issue warrants further investigation.

Study II was also the first to directly compare hippocampal volumes across both CH and HYPO groups relative to typically developing controls. Mild bilateral reductions in total hippocampal volumes (and each hippocampal sub-region) were found in HYPO participants, but not in children with CH. This finding corresponds with animal research suggesting that early prenatal TH deficiency, due to maternal hypothyroidism, may be associated with more significant and permanent alterations in hippocampal structure than late prenatal or postnatal TH deficiency due to CH (Ausó et al., 2004; Hasegawa et al., 2010; Lavado-Autric et al., 2003; Madeira et al., 1992). However, given the paucity of studies examining hippocampal volumes in children with early TH deficiency, our results require replication using larger sample sizes of CH and HYPO participants (i.e., > 20 per group). Interestingly, greater severity of maternal TH deficiency during the third trimester was found to significantly predict smaller anterior
hippocampal volumes and poorer delayed visuospatial memory scores in HYPO participants. This finding suggests that late prenatal TH deficiency, which affects both CH and HYPO groups, may lead to specific abnormalities within the anterior hippocampus as well as poor encoding and/or retrieval of visuospatial information. Contrary to our expectations, no significant relation between hippocampal volumes and episodic AM recall performance was found in children with early TH deficiency or typically developing controls. Given that previous studies found significant relations between reduced hippocampal volumes and episodic AM impairments in patient populations using alternate measures of episodic AM (i.e., the AMI and TEMPau task; Gilboa et al., 2005; Noulhiane et al., 2007), we questioned whether our measure of episodic AM (i.e., total episodic details recalled) provided the most sensitive assessment of episodic AM impairments and hippocampal dysfunction in clinical pediatric populations. Thus, Study III was conducted in order to address this concern.

Study III investigated the accuracy of episodic AM recall in both children with early TH deficiency and typically developing controls between 10 and 14 years of age. Given that one of the major limitations of Studies I and II was our inability to independently verify the original details of children’s AMs, a staged autobiographical event (i.e., a tour of SickKids) was created in order to address this limitation and examine group differences in accurate AM recall using the CAI. In addition, we focused on proportion accuracy scores (i.e., the percentage of total episodic details that were accurately recalled) in order to control for total verbal output and any possible group differences in language ability. Results from the CAI indicated that both CH and HYPO groups recalled significantly fewer accurate details and had lower proportion accuracy scores for the staged event than did typically developing controls. These findings are consistent with the results of previous studies that used staged events to assess impairments in AM accuracy in other clinical pediatric populations (e.g., children with autism or intellectual disability; Agnew & Powell, 2004; Bruck et al., 2007). Interestingly, lower proportion accuracy scores in CH and
HYPO groups were significantly associated with smaller anterior hippocampal volumes as well as greater severity of TH deficiency during the third trimester for HYPO and at birth for CH. These finding correspond with our results from Study II showing that more severe TH deficiency during late gestation is associated with specific reductions in anterior hippocampal volumes. Thus, late prenatal and very early postnatal TH deficiency may have important long-term consequences for the development of the anterior hippocampus, as well as for episodic AM accuracy performance.

Study III also revealed that greater visualization of autobiographical events at the time of recollection (i.e., as measured by participants’ self-report ratings) was associated with more accurate episodic AM recall, particularly the retrieval of accurate visual details, in both TH-deficient and control groups. This finding is similar to the results found in Study I in a large sample of typically developing children showing that visuospatial imagery is an important component of episodic AM. Contrary to our results in Study II, no significant group differences were found in hippocampal volumes in this study, possibly due to differences in sample size of the HYPO group across studies (i.e., N = 20 for Study II and N = 15 for Study III) and the fact that treated TH deficiency appears to have only mild adverse effects on hippocampal volumes that may be difficult to reliably detect. However, we did find that across all participants, smaller hippocampal volumes significantly predicted lower proportion accuracy scores, but not fewer total episodic details recalled from the staged event. This finding suggests that proportion accuracy scores, which control for total verbal output and assess only accurate episodic AM retrieval, may provide a more sensitive measure of children’s episodic AM ability, as well as hippocampal dysfunction in clinical pediatric populations, than the total number of episodic details reported.

Finally, given that volumetric measurements provide little insight into hippocampal function, Study IV was conducted to investigate hippocampal activation during episodic and
semantic AM retrieval in both typically developing children and children with early TH deficiency between the ages of 9 and 11. Importantly, this study was the first to use fMRI to investigate AM retrieval in children. Using a modified version of Maguire et al.’s (2000; 2001) sentence verification task, we found that both TH-deficient and control groups showed greater activation of the hippocampus and parahippocampal gyrus (PHG) during episodic AM retrieval than during semantic AM retrieval. This finding is consistent with previous studies showing that the hippocampus and PHG are preferentially active during episodic AM retrieval in adults and are critical regions in the AM neural network (Maguire & Mummery, 1999; Maguire et al., 2000; Svoboda & Levine, 2009). In addition, we found that both TH-deficient and control groups exhibited bilateral recruitment of the hippocampus and PHG during episodic AM retrieval as opposed to the left-lateralized pattern of activation commonly observed in young adults (Maguire & Mummery, 1999; Svoboda et al., 2006). Interestingly, Maguire and Frith (2003) observed a similar pattern of bilateral hippocampal activation in older adults, relative to younger adults. These researchers suggested that greater bilateral recruitment of core regions of the AM neural network may reflect neural compensation for age-related declines in episodic AM retrieval and the functional integrity of the AM neural network. Thus, our findings of bilateral hippocampal recruitment in 9 to 11 year-old children may signify neural compensation due to ongoing development of episodic AM as well as immature functioning of the AM neural network.

Study IV was also conducted in order to investigate whether early TH deficiency is associated with abnormal hippocampal function during AM retrieval. Results indicated that compared to typically developing controls, the TH-deficient group exhibited greater bilateral recruitment of the hippocampus and PHG during episodic AM retrieval, but not during semantic AM retrieval. In addition, the regression analyses revealed that smaller total hippocampal volumes and greater severity of early TH deficiency in the TH-deficient group predicted increased activation within the left hippocampus and PHG during episodic AM retrieval. Given
that the groups did not differ in performance on the fMRI task, our results suggest that children with early TH deficiency require greater recruitment of the hippocampus and PHG in order to reach the same performance level as controls. Alternatively, hyperactivation of the hippocampus and PHG in the TH-deficient group could also be a marker of the adverse effects of early TH deficiency on hippocampal function later in life. Importantly, our results are consistent with Maguire et al.’s (2001) study showing bilateral recruitment of the hippocampus during episodic AM retrieval in patient Jon, as well as other fMRI studies showing hyperactivation of the hippocampus and PHG in patients with mild cognitive impairment and hippocampal abnormalities (Hämäläninen et al., 2006). Finally, we also found that in the TH-deficient group, greater visualization of past events during scanning predicted greater activity within the hippocampus and PHG during episodic AM retrieval. Given that higher visualization ratings were associated with better episodic AM recall and accuracy performance in Studies I and III, our results from Study IV suggest that visuospatial imagery may enhance one’s ability to reexperience and successfully recall episodic AM details by increasing activation within the hippocampus and PHG during episodic AM retrieval. Overall, the findings from Studies II-IV suggest that early TH deficiency has significant long-term consequences for children’s episodic AM performance, as well as hippocampal structure and function.

6.2 General Limitations

Overall, this dissertation has two main limitations beyond those discussed in the previous chapters describing individual studies. First, it is well known that episodic AM is a complex memory phenomenon that draws on a number of diverse cognitive processes and an entire network of brain regions, enabling one to encode, store, and retrieve many different types of details from specific past events (Addis et al., 2004; Conway & Rubin, 1993; Daselaar et al., 2008; Svoboda et al., 2006). Due to the targeted nature of our goal to focus on the hippocampus...
and its critical role in episodic AM during childhood, it was beyond the scope of the present dissertation to investigate the role of other core regions of the AM neural network, such as the prefrontal cortex or parietal regions involved in visuospatial processing, or to conduct whole-brain connectivity analyses in order to examine functional interactions between these regions and the hippocampus during episodic AM retrieval. As a result, it is important to acknowledge that the work presented in this dissertation can only speak to the specific role of the hippocampus in episodic AM during childhood, despite the fact that the hippocampus does not operate in isolation (Maguire et al., 2000). This limitation is significant because the present dissertation also focuses on the effects of early TH deficiency, which is known to have adverse effects on several core regions of the AM neural network, including the cerebral cortex, thalamus, and cerebellum, depending on the exact timing of TH loss (Bernal & Nunez, 1995; Chan & Rovet, 2003). Thus, any conclusions drawn from this dissertation about the effects of early TH deficiency on episodic AM and hippocampal function during childhood, are limited by our inability to investigate interactions between core regions of the AM neural network. Clearly, future studies are required in order to replicate and expand on the present findings.

The second general limitation of the present dissertation is that it is impossible to disentangle whether the weaknesses in episodic AM observed in children with early TH deficiency reflect: (a) poor encoding and binding of contextual details at the time of the event, (b) poor retrieval of these details at the time of testing, or (c) a combination of these two impairments. The hippocampus is well known for its role in memory formation and the binding of contextual information available at the time of encoding into a sustainable memory trace (Buckner & Wheeler, 2001; Eichenbaum & Bunsey, 1995; Lipton & Eichenbaum, 2008). However, the hippocampus also plays an important role in successful memory retrieval, acting as a ‘hub’ or convergence zone for reintegrating and re-experiencing contextual details (Addis et al., 2007; Eldridge et al., 2000; Moscovitch, 2008). Given that early TH deficiency significantly
impairs hippocampal development very early in life, it is possible that the conditions described presently are associated with weaknesses in both memory encoding and retrieval. However, because this dissertation was not specifically designed to compare memory encoding and retrieval, further investigations using both behavioural and neuroimaging techniques are required in order to examine the effects of early TH deficiency on these separate memory processes.

6.3 Implications of Findings

Despite the limitations listed above, the findings presented in this dissertation have several important implications for studying AM in typically developing children, and for our current understanding of the effects of early TH deficiency on the hippocampus and episodic AM performance. First, this dissertation indicates that the newly-developed Children’s Autobiographical Interview (CAI) is a particularly useful tool for investigating episodic and semantic AM recall, as well as AM accuracy performance (i.e., when combined with a staged event), in both typically developing children and clinical pediatric populations. As a result, this tool could be used in future studies to examine episodic and semantic AM recall, AM accuracy, and the ability to retrieve specific types of episodic details (e.g., visual, spatial, temporal, emotional, etc.) in other clinical pediatric populations with hippocampal damage, such as children with temporal lobe epilepsy and children with developmental amnesia. In fact, studies using the CAI to investigate AM performance in children with temporal lobe epilepsy (S. Lah, personal communication, June 1, 2011) and in children with fetal alcohol spectrum disorders (S. Agnihotri, personal communication, December 38, 2010) are currently underway. In addition, given that the CAI is only a slightly modified version of Levine et al.’s (2002) Autobiographical Interview for adults (see Appendix A for a comparison between the two measures), data collected in children using the CAI could be easily contrasted to data collected in adults using the Autobiographical Interview in order to investigate: (a) changes in AM across the lifespan, from
early childhood to old age; and (b) differences in AM performance between child and adult patient groups, such as cases of prenatal TH deficiency versus adult-onset hypothyroidism, or childhood-onset versus adult-onset temporal lobe epilepsy.

Second, our results indicated that early TH deficiency appears to have a similar, albeit much less severe, impact on episodic AM and the integrity of the hippocampus as other conditions associated with episodic AM impairments and hippocampal dysfunction. For example, children with early TH deficiency exhibited a similar pattern of impaired episodic AM but preserved semantic AM and general semantic memory as patients with developmental amnesia and temporal lobe epilepsy (e.g., Maguire et al., 2001; St-Laurent et al., 2009; Vargha-Khadem et al., 1997). In addition, our HYPO participants exhibited bilateral reductions in hippocampal volume, which were also found in Issacs et al.’s (2000) study of children born prematurely as well as Maguire et al.’s (2001) case study of patient Jon. Finally, both CH and HYPO groups exhibited greater bilateral hippocampal activation during episodic AM retrieval relative to controls, and patient Jon with developmental amnesia also exhibited bilateral hippocampal activation during episodic AM retrieval (Maguire et al., 2001). Thus, our results highlight the importance of TH for normal hippocampal development and indicate that early TH deficiency is an important condition to study in order to investigate the effects of abnormal hippocampal development on episodic AM performance.

Third, it was surprising that CH and HYPO participants were indistinguishable across Studies II to IV in terms of their episodic AM recall and accuracy performance, as well as their patterns of hippocampal activation during AM retrieval, despite the fact that they experienced only a slight overlap in the timing of their early TH deficiency (e.g., during late gestation). Based on animal research suggesting that early prenatal TH deficiency may be associated with greater abnormalities in hippocampal structure (Ausó et al., 2004; Hasegawa et al., 2010; Lavado-Autric et al., 2003; Madeira et al., 1992), and our finding that only HYPO participants exhibited
reduced hippocampal volumes in Study II, we could have expected greater impairments in episodic AM and hippocampal function in HYPO relative to CH. On the other hand, we also could have expected greater impairments in episodic AM and hippocampal function in CH participants, given that most of these children were inadequately monitored and treated throughout childhood (see Figure 3.2) and they exhibited lower IQ scores than controls. Importantly, however, animal models of CH and HYPO conditions have shown that despite being associated with different structural abnormalities within the hippocampus, both conditions result in similar impairments in synaptic function as well as memory deficits (Liu et al., 2010; Reid et al., 2007). In addition, our results showing that both CH and HYPO conditions are associated with poor retrieval of visual details from past events, as well as poor delayed visuospatial memory (i.e., from the Rey-O), are consistent with previous studies showing that both CH and HYPO groups exhibit similar deficits in visuospatial abilities (Man et al., 1991; Mirabella et al., 2005; Oerbeck et al., 2005; Rovet, 1999). It also important to note that no study has specifically compared memory function across both CH and HYPO groups. Thus, the findings in this dissertation are unique because they indicate for the first time that CH and HYPO groups exhibit similar impairments in episodic AM and similar abnormalities in hippocampal function that appear to be associated with late prenatal TH deficiency. However, further investigation into the timing effects of early TH deficiency using more consistent testing of maternal TH levels throughout pregnancy in hypothyroid women, as well as TH levels across the first few months of life in children with CH, is required.

This dissertation also has important implications for the treatment of maternal hypothyroidism during pregnancy as well as CH throughout childhood. Our findings indicated that children whose mothers were treated for hypothyroidism during pregnancy, and children with early-treated CH, exhibit significant weaknesses in episodic AM recall and accuracy, reduced hippocampal volumes (in HYPO only), as well as abnormalities in hippocampal
function, relative to typically developing children. In addition, most CH participants exhibited elevated TSH values throughout infancy and childhood (see Figure 3.2), signifying that they received inadequate TH treatment and were exposed to mild TH deficiency during this period. These findings imply that both maternal and congenital hypothyroidism conditions have not been adequately treated and require more vigilant and frequent monitoring of TH and TSH levels. Fortunately, new guidelines for the management of maternal hypothyroidism are soon to be published (De Groot et al., in press) and several researchers have urged for better treatment programs for children with CH, especially those with more severe CH etiologies (Kempers et al., 2006; Oerbeck et al., 2005; Rovet, 2005).

Finally, our results also demonstrated that the developing hippocampus is very sensitive to damage because even mild cases of early TH deficiency (i.e., due to inadequate treatment) led to reduced hippocampal volumes in HYPO and abnormal hippocampal functioning in both CH and HYPO groups. According to Bachevalier and Vargha-Khadem (2005), there is little recovery of function following severe hippocampal damage sustained very early in life, as few other brain regions or neural circuits can serve as substitutes for the hippocampus and its critical and complex role in memory. As a result, this dissertation also serves to increase awareness about the effects of early TH deficiency so that earlier diagnosis and more aggressive treatment programs for maternal hypothyroidism during pregnancy, as well as CH, may one day prevent or attenuate the memory impairments and hippocampal abnormalities associated with these two conditions.

6.4 Future Directions

Although the research presented in this dissertation has provided critical new insight into episodic AM performance and hippocampal structure and function in children with early TH deficiency and typically developing children, several important questions remain unanswered. As mentioned previously, further research is required in order to investigate the development and
function of the AM neural network in typically developing children. In particular, it remains unclear how the development of episodic AM across childhood and adolescence is specifically influenced by the prolonged maturation of brain regions that critically support episodic AM, such as the hippocampus and prefrontal cortex. Thus, longitudinal studies that use both behavioural and neuroimaging techniques to track age-related changes in episodic AM and functional connectivity within the AM neural network would be extremely useful to better understand structure-function relations in AM across development. Once this information in typically developing children is obtained, additional studies can then be conducted to investigate how early insult to the hippocampus alters functional connectivity within the AM neural network.

Further neuroimaging research is also required to investigate the integrity and volume of the CA fields and dentate gyrus in both offspring of hypothyroid women and individuals with CH, given that animal studies have shown that these two subregions are differentially affected by the timing of early TH deficiency (Ausó et al., 2004; Gilbert & Paczowski, 2003). Recent evidence indicates that high resolution in vivo scanning using a 7.0T field strength is feasible in humans using clinically acceptable scanning durations (e.g., 10-15 minutes) and allows for significantly better visualization of hippocampal subregions (e.g., down to 100 μm) than classic 1.5T and 3.0T scanners (Cho et al., 2010; Thomas et al., 2008; Prudent et al., 2010). In fact, several studies have already used 7.0T scanners to investigate the integrity of hippocampal subregions in patients with temporal lobe epilepsy (e.g., Breyer et al., 2010) and patients with Alzheimer’s disease (e.g., Kerchner et al., 2010). Although there are few 7.0T scanners currently available for research and there are some limitations associated with 7.0T scanning (e.g., greater susceptibility artifacts), the use of high resolution imaging is a promising technique that could facilitate accurate volumetric analysis of hippocampal subregions and identify abnormalities in the cytoarchitecture of these subregions in individuals who experienced early TH deficiency.
In addition, given that animal studies have shown that prenatal TH deficiency significantly impairs neuronal migration, resulting in an increased number of heterotopic neurons within the hippocampus and subcortical white matter (Ausó et al., 2004; Berbel et al., 2010; Cuevas et al., 2005; Lavado-Autric et al., 2003), it may be beneficial to further examine the effects of early TH deficiency on hippocampal integrity and connectivity using diffusion tensor imaging (DTI). DTI is an MRI technique that examines brain structure by measuring the diffusion of water within white matter tracts (Powell et al., 2004). This technique has already been used to examine diffusion abnormalities within the hippocampus in patients with temporal lobe epilepsy (e.g., Salmenpera et al., 2006) and to examine the development of structural connections between the hippocampus, medial prefrontal cortex, and posterior cingulate in typically developing children (e.g., Supekar et al., 2010). Thus, future studies could use DTI to investigate whether children with early TH deficiency exhibit diffusion abnormalities within the hippocampus as well as abnormal connections between key regions of the AM neural network.

Finally, given that this dissertation is the first investigation of AM in individuals who experienced early TH deficiency, our results require replication and further exploration of AM performance within this population. In particular, because we consistently found weaknesses in the ability to retrieve visual details in both CH and HYPO groups, one important avenue for future research would be to investigate the effects of early TH deficiency on: (a) the ability to encode and retrieve visual episodic details, (b) visual imagery during episodic AM retrieval, (c) the development of brain regions involved in both visuospatial processing and episodic AM retrieval, such as the posterior cingulate and visual cortex; and (d) functional and structural connectivity between these regions and the hippocampus. In addition, given that several animal and human studies have shown that adult-onset hypothyroidism is also associated with significant memory impairments (e.g., Alzoubi et al., 2009; Fernández-Lamo et al., 2009; Miller et al., 2006; Tong, Chen, Liu, & Zhou, 2007), future studies could also compare AM and general
memory abilities in individuals with adult-onset hypothyroidism to those with prenatal or early postnatal TH deficiency in order to further examine how the exact timing of TH deficiency affects different memory abilities. Furthermore, because our CH and HYPO participants exhibited significant weaknesses on a ‘real-world’ measure episodic memory (i.e., the CAI) but not on a laboratory/clinical test of verbal episodic memory (i.e., story recall) in Study II, it may also be interesting to examine whether individuals with TH deficiencies also show weaknesses in other ‘real-world’ memory functions that depend on the hippocampus, such as prospective memory (i.e., remembering to perform tasks in the future), imaging future events, and spatial navigation (Addis, Wong, & Schacter, 2007; Maguire, Nannery, & Spiers, 2006).

6.5 General Conclusion

In conclusion, the purpose of this dissertation was to investigate the effects of early TH deficiency on episodic AM performance and the integrity of the hippocampus using a combination of both behavioural and neuroimaging methods. This research is unique in that it was the first to examine AM recall and accuracy performance in children with abnormal hippocampal development, using the newly-developed Children’s Autobiographical Interview as well as a novel staged autobiographical event. In addition, this dissertation is the first to examine hippocampal activation during episodic and semantic AM retrieval in both typically and atypically developing children using fMRI. The results indicated that children who were exposed to insufficient TH levels early in life exhibited weaknesses in episodic AM recall and accuracy, reduced hippocampal volumes (in HYPO only), as well as abnormal functioning of the hippocampus during episodic AM retrieval, relative to typically developing controls. Overall, this dissertation contributes substantially to our current understanding of the effects of early TH deficiency on hippocampal structure and function, and provides critical new insight in episodic and semantic AM performance in children with hippocampal abnormalities.
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Appendices

Appendix A

*Comparison Between the Children’s Autobiographical Interview and Levine et al.’s (2002)*

**Autobiographical Interview for Adults**

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Provided Instructions?</td>
<td>Yes (see Appendix B)</td>
<td>Yes (see Levine et al., 2002)</td>
</tr>
<tr>
<td>Number of AMs assessed</td>
<td>2</td>
<td>5</td>
</tr>
<tr>
<td>Queried specific time periods?</td>
<td>No, only the last few years</td>
<td>Yes: 5 time periods for older adults (early childhood, adolescence, early adulthood, middle age, and the previous year) and 4 for younger adults (no middle age time period)</td>
</tr>
<tr>
<td>Provided Sample AM Event List?</td>
<td>Yes: 18 (see Appendix C)</td>
<td>Yes: 100 across all time periods</td>
</tr>
<tr>
<td>Included Recall, General Probe, and Specific Probe Phases?</td>
<td>Yes (identical to the AI)</td>
<td>Yes</td>
</tr>
<tr>
<td>Included participant self-report ratings?</td>
<td>Yes: 7 (emotional change, personal importance now and then, visualization, rehearsal, strength, and confidence)</td>
<td>Yes: 5 (emotional change, personal importance now and then, visualization, rehearsal)</td>
</tr>
<tr>
<td>Used the Autobiographical Interview Scoring Manual?</td>
<td>Yes (identical to the AI)</td>
<td>Yes</td>
</tr>
</tbody>
</table>
Appendix B

*Instructions for the Children’s Autobiographical Interview from Study I*

“I am going to ask you to tell me about two events that have happened to you in the past. Here is a list of some events that might be of help. You can choose two events from this list or you can choose two different events that are not on this list. There are three rules to follow when you are choosing your two events. First, you can pick an event from any time in your life, as long as it happened more than one month ago because I don’t want you to describe something that just happened (i.e., a very recent event). The second rule is that the events that you choose have to be ones where you were personally there and you took part in what happened. Do not pick events that you have only heard about from your parents, family, or friends, or only saw in a photograph, they must have happened to you. Finally, the third rule is that I want you to pick an event that happened at a specific time and place. You should pick an event that happened within a couple hours or one day at the most. For example, I don’t want you to describe a 3-week long vacation because that is not specific enough, however, you could tell me about something that happened on one day during your vacation. I will ask you to describe one event first, then the other one. Then I will ask you some questions about both events. I would like you to give me as much detail about what happened as you can. I am not interested in which events you choose, but I am interested in how you tell the event to me. So, try and pick events that you feel comfortable describing to me in detail. To help me remember what you said, I will be audiotaping your description of the event and your answers to the questions. Because your name is not on the tape it will be completely confidential and it will be stored in a locked cabinet so that no one else has access to it. Is that okay? Do you have any questions?”
Appendix C

*Sample Autobiographical Events Provided to Participants to Facilitate AM Retrieval*

Choose events that happened to you in a specific time and place more than one month ago.

For example, you could choose…

- Your last birthday
- A school trip
- A sporting event
- Halloween
- Getting your first pet
- Your first sleepover
- Winning an award
- Going to a concert
- First time on a plane or a train
- Something that happened on one day of a vacation
- A wedding
- Your first time riding a bike
- Moving to a new home
- Your graduation
- A school party or dance
- A boat ride
- A holiday party
- Your performance in a play, recital, or band
Appendix D

Scoring Example Using the Autobiographical Interview Scoring Manual

<table>
<thead>
<tr>
<th>Event</th>
<th>Place</th>
<th>Time x 2</th>
<th>Perceptual</th>
</tr>
</thead>
<tbody>
<tr>
<td>“We went white water rafting in B.C. in August, 2008. The water was freezing.”</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Emotional</td>
<td>Semantic</td>
<td>Other</td>
<td></td>
</tr>
<tr>
<td>I was really nervous because I had never done it before. I can’t remember the</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Repetition</td>
<td>External Event</td>
<td>External Event (Time)</td>
<td></td>
</tr>
<tr>
<td>name of the river, I was so nervous. We went rafting again last summer.</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Composites:

Episodic Details (i.e., sum of Event, Place, Time, Perceptual, Emotional details)

Non-episodic Details (i.e., sum of Semantic Facts, Other Metacognitive Statements, Repetitions, External Event details)
Appendix E

Descriptions and Examples of Experimenter Ratings using the Autobiographical Interview Scoring Manual

<table>
<thead>
<tr>
<th>Rating</th>
<th>Sub-Category</th>
<th>Description</th>
<th>Scale</th>
<th>Examples</th>
</tr>
</thead>
</table>
| **Experimenter Rating Composite** | Episodic Richness | Assesses the overall richness with which an episode is described            | 0 – 6 | **5-6 points:** provided a response that is rich in detail, containing at least 2 elaborations, and evokes an impression of true re-experiencing. *See the Autobiographical Interview Scoring Manual for a detailed example.*  
**3-4 points:** provided a response that had moderate detail and contained at least two elaborations. *See the Autobiographical Interview Scoring Manual for a detailed example.*  
**1-2 points:** provided a response with limited detail and/or limited elaboration of events. *E.g., I got stung by a bee at school. When I went outside, it stung me on the ear and that’s it.*  
**0 points:** provided no episodic information |
| Place                         |                    | Assesses localization of a specific location                                | 0 – 3 | **3 points:** provided enough specific details to re-create a setting within a few meters and the response is tied to some global/contextual information. *E.g., breakfast table in hotel’s restaurant in Banff, B.C.*  
**2 points:** provided some specific detail but lacking global information or some larger scale information but lacking precise localization. *E.g., restaurant in Banff*  
**1 point:** provided a general location without specific detail or a specific location without any context. *E.g., in B.C.*  
**0 points:** did not provide any place information |
| Time                          |                    | Assesses the localization of the remembered event within a specific time frame | 0 – 3 | **3 points:** provided year, month/season, and hour/time of day. *E.g., February morning in the 6th grade*  
**2 points:** provided at least 2 pieces of information about the time, but lacking specific or global context. *E.g., winter during grade 6*  
**1 point:** provided minimal/vague temporal details. *E.g., winter during elementary school*  
**0 points:** did not provide any time information |
| Perceptual Richness | Assesses perceptual details within the following 6 modalities: taste, auditory, visual, olfactory, tactile/pain, and spatial-temporal | 0 – 3 | **3 points**: provided at least 2 different modalities and the response reflects the ability to re-experience some aspect of at least one percept. *E.g.*, seeing a pink dress with lace around the collar (visual vividness)  
**2 points**: provided 2 or more perceptual details that were lacking in richness or a feeling of re-experiencing  
**1 point**: provided 1 or more perceptual details that lack richness or provided some perceptual detail that was not directly related to the event. *E.g.*, a pink dress  
**0 points**: did not provide any perceptual information |
| Emotions and Thoughts | Assesses the extent to which a person is able to recreate what he/she was thinking and/or feeling at the time the event occurred | 0 – 3 | **3 points**: provided a response that reflected the specific cognitive and/or emotional state of the subject at the time of the event. *E.g.*, I was very upset at the sleepover because my friend was moving away the next day and I wanted to spend more time with her  
**2 points**: provided 1 or more thoughts/feelings but the response only partially captures the specific cognitive and/or emotional state at that time. *E.g.*, I was very nervous when the ceremony started  
**1 point**: provided 1 or more thoughts/feelings that did not capture the key emotional/cognitive state of the subject at the time of the event. *E.g.*, I wanted to go  
**0 points**: did not provide any emotion/thought information |
| Time Integration | n/a | 0 – 3 | **3 points**: the episode was linked to a larger time frame by describing some specific contextual information about at least one event that occurred before or after the recalled event. *E.g.*, I went to Walt Disney World a month before I started grade 5  
**2 points**: richly described one or more events that occurred before/after the recalled episode and provides specific contextual information, but there is no link to a more global time frame. *E.g.*, I went home afterwards and called my friend to apologize  
**1 point**: described one or more events that occurred before/after the recalled episode but the description is limited in terms of specific contextual details and is lacking global integration. *E.g.*, she went home  
**0 points**: no evidence of integrating the event into a larger time scale |

This chart is adapted from the Autobiographical Interview Scoring Manual with permission from Brian Levine.
Appendix F

**Skewness and Kurtosis Values for Variables that were Significantly Deviated in Study I**

<table>
<thead>
<tr>
<th>Variable:</th>
<th>Before Log10 Transformation</th>
<th>After Log10 Transformation</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Skewness</td>
<td>Kurtosis</td>
</tr>
<tr>
<td><strong>Recall Condition</strong></td>
<td>Statistic (SE)</td>
<td>Statistic (SE)</td>
</tr>
<tr>
<td>Total episodic details</td>
<td>1.93 (0.18)</td>
<td>3.87 (0.36)</td>
</tr>
<tr>
<td>Event details</td>
<td>2.03 (0.18)</td>
<td>4.64 (0.36)</td>
</tr>
<tr>
<td>Emotion/thought details</td>
<td>2.08 (0.18)</td>
<td>4.24 (0.36)</td>
</tr>
<tr>
<td>Repetitions</td>
<td>1.71 (0.18)</td>
<td>3.19 (0.36)</td>
</tr>
<tr>
<td>External event details</td>
<td>2.30 (0.18)</td>
<td>4.70 (0.36)</td>
</tr>
<tr>
<td><strong>Recall + Specific Probe Condition</strong></td>
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<td></td>
</tr>
<tr>
<td>Event details</td>
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</tr>
<tr>
<td>Semantic details</td>
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<td>2.53 (0.36)</td>
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<tr>
<td>Repetitions</td>
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<td>External event details</td>
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<tr>
<td><strong>Other Variables</strong></td>
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<td></td>
</tr>
<tr>
<td>Retention Interval</td>
<td>1.46 (0.18)</td>
<td>2.30 (0.36)</td>
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</table>
### Appendix G

**Skewness and Kurtosis Values for Variables that were Significantly Deviated in Study II**

<table>
<thead>
<tr>
<th>Variable:</th>
<th>Before Log10 Transformation</th>
<th>After Log10 Transformation</th>
</tr>
</thead>
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<td></td>
</tr>
<tr>
<td>Time details</td>
<td>Skewness Statistic (SE) 1.44 (0.27) Kurtosis Statistic (SE) 2.20 (0.54)</td>
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<tr>
<td>Total non-episodic details</td>
<td>Skewness Statistic (SE) 1.59 (0.27) Kurtosis Statistic (SE) 2.27 (0.54)</td>
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</tr>
<tr>
<td>Repetitions</td>
<td>Skewness Statistic (SE) 1.66 (0.27) Kurtosis Statistic (SE) 2.48 (0.54)</td>
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</tr>
<tr>
<td>External event details</td>
<td>Skewness Statistic (SE) 2.82 (0.27) Kurtosis Statistic (SE) 7.18 (0.54)</td>
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<td></td>
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<tr>
<td>External event details</td>
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<td>Maternal TSH Trimester 3</td>
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<td>Average Childhood TSH</td>
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<td>Skewness Statistic (SE) -0.45 (0.47) Kurtosis Statistic (SE) 0.83 (0.92)</td>
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Appendix H

Non-Parametric Mann-Whitney Tests for Group Differences in AM Performance in Study II

<table>
<thead>
<tr>
<th>Variable</th>
<th>Mann-Whitney test statistic (U)</th>
<th>z-score</th>
<th>p-value</th>
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<tr>
<td><strong>Recall Condition:</strong></td>
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<td></td>
</tr>
<tr>
<td>Total episodic details</td>
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<td>.001</td>
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<td>.003</td>
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<td>.090</td>
</tr>
<tr>
<td>Time details</td>
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<tr>
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<td>Emotion/Thought details</td>
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<td>Total non-episodic details</td>
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Note: Variables in *italics* represent those that were significantly non-normal on the Kolmogorov-Smirnov test. These results are identical to those reported in Study II using parametric tests.
Appendix I

Boxplots across groups for hippocampal volume, delayed visuospatial memory, and severity of maternal TH deficiency variables
Appendix J

Instructions for the Staged Autobiographical Event in Study III

“This lunch break is going to be part of a memory experiment later on, which means that the next time you come in to do our study in about four months from now, I’m going to ask you some questions about what we did during this lunch break and get you to describe all the details you can remember about it. So I’d like you to pay very close attention to everything that happens within the next 45 minutes. You should try your best to remember what things we do during lunch, what we talk about, where we go, what things look like, and any smells, sounds, or tastes. Do you understand these instructions? If you have any questions along the way just let me know. Okay, first we’re going to go down to the cafeteria on the Main floor and you can pick out a lunch there. I’ll give you 10 dollars to pay for lunch. Along the way I’m going to ask you a couple questions and point out a few things. Basically, I’ll be giving you a short tour of the hospital. And then we’re going to come back up here to our lunch room and you can pick out a video to watch while you eat your lunch. Do you have any questions? Okay, let’s go.”
Appendix K

Staged Event Instructions and Examiner Script for Study III

Materials: Examiner wears a solid colour shirt/sweater and their badge

Part I: 5-10 minutes

1) Meet child in testing room. Introduce yourself “Hi my name is ___________” (make sure they hear your name clearly). Ask them for their name and record it along with their subject number and gender on the Staged Event Info Sheet. Read them the provided instructions.

2) On your way out of the interview room, tell them the time by saying something like, “Let’s see how much time we have. Okay it is (11:45), we’ve got exactly 45 minutes for lunch.”

3) Ask them their birth date and grade and enter it on the Staged Event Info Sheet.

4) Ask them if they know the date and the day of the week (if they don’t know, tell them the date and day of the week & fill it in on the Info Sheet).

5) Describe your route as you walk “Okay now we’re going to turn left here and go down this hallway to get to the glass elevators, which will take us down to the Main floor.”

6) Ask “Do you know what floor we’re on?” Also ask them, “Do you know what wing we were just in?” (if they don’t know, tell them the answers).

7) Ask, “Do you know what the address of SickKids hospital is?” Allow them to respond, if they don’t know tell them “It’s a pretty easy address to remember because all the numbers are the same, its 555 University Avenue.”

8) When you enter the hallway with windows on either side, stop in the middle and say, “Okay, we’re going to stop here for a second. Since we’re not going to get a chance to go outside today, I want you look out these windows and describe to me what the weather looks like outside.” Ask them what colour the sky is, what temperature they think it is, etc. Record their description and use this time to record what they are wearing (e.g., jeans).

9) Ask “Have you been in the glass elevators before?” and ask “When was the last time you were at SickKids?” and record their answers.

10) Before you go in the glass elevators, walk to the left side of the atrium so that you can look down to the main floor and clearly see the clock on the north wall and the pig/cow statue hanging in the middle. Say “Okay, before we go down to the cafeteria, we’re going to play a quick game. It is sort of like playing 20 questions. I’m going to pick an object from somewhere in front of us, and you are going to try and guess what it is by asking me yes or no questions. For example, you could ask me if the object is a certain colour, or if it is on a certain side of the room. Do you understand? Okay, I’ve got an object in mind (the pink pig statue), try and guess what it is. (if they don’t guess it within 10 tries say “that’s okay, I was thinking about the pig, but you still have one more try”). “Okay great, now I’m going to pick one more object (the red clock on the wall), try and guess what it is.” Once they’ve guessed the clock say “Yes, that’s right. Can you tell me what time it is on the clock?” Record the time on the info sheet. (If they don’t get it right, tell them you were thinking of the clock and ask them the time. If they don’t tell you the correct time, tell them the correct answer but record both their response and the correct time).

11) Say, “Okay, now you get a chance to pick an object and I’ll see if I can guess it – but this time, let’s look on the right side of the atrium.” Move across the hallway and look down on the right side of the atrium, and play one more round. (This is just to give them more opportunity to take in the visual scene – it doesn’t matter what object they pick). If you can’t guess within 10 questions, say you give up and get them just to tell you.

12) Go to the elevators, let them press the button down. Ask, “Are you afraid of heights?” and record their answer.
Part II: 5-10 minutes
13) When you get out of the elevator say, “There’s a couple different places you can go for lunch. There’s Subway over here. Let me show you what’s in the cafeteria too. There’s pizza pizza here or you could get a sandwich or soup. What do you think you want for lunch? Don’t forget to get a drink too.” (make sure they walk through the cafeteria first).
14) Once they’ve picked their lunch, give them a 10 dollar bill and let them pay. Make note of what they bought for lunch (the drink too), and how much the lunch cost. Take back any of the large change (bills, toonies, loonies, and quarters) but let them keep the other change and tell them we’ll use the change in just a second.
15) Ask them how much change they have and record it on the sheet (if they didn’t get any change, give them a couple pennies and nickels that you’ve brought along).
16) Tell them they can either donate their change into the box for the sick kids foundation (right beside the elevators) or they can throw the change into the fountain, or do both if they wish.
17) Then walk towards the black wing via Main Street. Before you pass the footprints on the floor by Starbucks, say, “See those footprints on the floor? They go all the way from here to the end of this hallway where that 3rd Main Street sign is hanging. How many footsteps do you think there are in this hallway?” record their answer. “Okay, let’s count them as we walk through and see how close your guess was.” Record the actual number.
18) Then say, “Okay, now we’re going back into the black wing of the hospital. I’ve just got one more thing to show you but we have to go up one floor to get there, to the first floor, so we’re going to turn right here and go up the stairs.”
19) Go up to the first floor using the closest stairwell and turn right. Stop at the wall display on the right side a few feet from the stairwell. Say, “This is a display of all the objects people have swallowed by accident at this hospital many, many years ago. Can you tell me what some of the objects are? (allow them time to look. If they don’t mention many, point out a few interesting ones for them). Ask them, “Can you guess why there are so many safety pins in this display?” Allow them to guess. If they don’t know why, or give another reason, say, “A long time ago, safety pins were a very common object to be swallowed by children because babies used to wear cloth diapers that were held together by safety pins, which could easily come undone and be swallowed.”
20) Say, “Okay, so now we’re done with our tour and we can go back up to the 6th floor to eat our lunch in the lunch room.” Take the Black Wing elevators to the lunch room.
Part III: 25-30 minutes
21) When you go into the lunch room, have them sit at the right side of the table facing the laptop. You should sit on the left side by the microwave. Get them to choose one video:
1) America’s Funniest Home Videos: Best of or Sports Edition; 2) Just for Laughs Gags
3) Mr. Bean; 4) News Bloopers
22) Record what time the video started and what you ate for lunch. Let them watch the video until the 45 minute lunch break is over. Record the time that the video ended. Say something like, “Okay, its 1pm, looks like lunch time is just about over, let’s stop the video.”
23) Point to the rosemary plant on the table and say, “Do you know what kind of plant this is?” If they don’t know say, “It’s a rosemary plant, which is used a lot in cooking.” Get them to smell the rosemary plant by saying, “Try smelling it. What you do is pick off a couple of the needles and break them in half and then smell it, like this. What do you think it smells like?” Record their response.
24) Say, “Alright, let’s go back and start the afternoon session of testing.”

Record down any other notable details from the lunch (e.g., did they see their parents at any time, did they leave the lunch room during the video, did you see anything unusual on the tour).
STAGED LUNCH: INFORMATION SHEET

Name of Participant (first only): ______________ Age: ___ Subject #: ______ Gender: ______

Date of Lunch (DD/MM/YYYY): (___ / __ / ______) Day of Week: ___________________

Start Location: __________ Start Time: ______ Birth Date (DD/MM/YYYY): (___ / ___ / ___)

Grade: _____ Participant knew date (and year)? (Y/N): ___ Day of the week?: (Y/N): _______


Participant’s description of weather outside (sky colour, temperature, etc.): ______________________

Participant’s clothing: ___________________________________________________________________

Did they correctly guess object 1? (Y/N): ______ Did they correctly guess object 2? (Y/N): ______

Time on clock in Atrium: __________ Object they picked in Atrium: _______________________

Been in glass elevators before? _____ Afraid of heights? ______ Last visit to Sickkids: _______

Participant’s lunch choice (give as much detail as possible, drink as well): ______________________

Cost of lunch? __________________________

Amount of donated change? __________ Did they put change in fountain or box? _____________

Guessed # of footprints: _______ Real # of footprints: _______ Objects described in display: 

____________________________________________________________________________________

Reason given for safety pins: __________________________

Time at start of Video: ___________ Time at end of Video: _______ Video Chosen: ___________

What the experimenter ate for lunch: _______________________________________________________

Colour of experimenter’s t-shirt/sweater: __________________________

Did they know what the plant was? (Y/N)? ____ Their description of the rosemary smell: ______

____________________________________________________________________________________

Any other notable details from event (e.g., if they stopped to talk to parent, if they went to the washroom, describe their demeanor, etc.): __________________________________________
Appendix L

Probing Questions from the Specific Probe Phase of the CAI for Study III

Note: Bold indicates additional questions about the staged event that were added for Study III

Specific Probe Phase:
1. When did this event take place? *If not enough information is given, probe with the following questions:*
   a) Do you remember what year it was?
   b) Do you remember the Month or Season?
   c) Do you remember the date or time of month?
   d) Do you remember the day of the week?
   e) Do you remember what time lunch started?
   f) Do you remember what time lunch ended?
   g) How old were you at the time?

2. Where did this event take place? *If not enough place information is given, probe with the following questions:*
   a) What province were you in?
   b) What city were in you?
   c) Do you remember what the address of the hospital was?
   d) Do you remember which floor you started on?
   e) Do you remember which wing you started in?
   f) Do you remember what floor the cafeteria was on?
   g) Do you remember where you ate your lunch?
   h) *If yes to question above (h), Do you remember where you were in the room (i.e. where you were sitting)? And Do you remember where I was while you were eating lunch?*

3. Are there any things or objects that stand out when you remember the event?

4. Do you remember any colours?

5. Do you remember any sounds?

6. Do you remember any smells?
   *If no, Do you remember smelling a plant in the lunch room?*
   *If yes then, Do you remember what you said it smelled like?*

7. Do you remember any tastes?
   *If no, Do you remember what you ate for lunch? (and drank?) Do you remember what I ate for lunch?*

8. Do you remember any physical feelings or sensations, like if you felt hot or cold or tired?

9. Do you remember your body position during the lunch break, like if you were sitting, standing, or moving?
10. Do you remember how long we watched the video for?

11. Do you remember any seeing anyone else beside me during the lunch hour?

12. Can you tell me anything about what you were thinking or feeling at the time?

13. Do you remember describing what the weather was like that day?
   *If yes,* what was your description?

14. Do you remember the game that you played before you got your lunch?
   *If yes,* What were the two objects that you had to guess? *And* Do you remember what colour they were? *And* What was the object that you picked for me to guess?

15. Do you remember what you did with the change left over after paying for lunch? *And* Do you remember how much change you had?

16. Do you remember guessing how many footprints there were on the floor?
   *If yes,* How many did you guess? *And* Do you remember how many were actually on the floor?

17. Do you remember looking at a display with objects people have swallowed?
   *If yes,* What were some of those objects? *And* Do you remember me saying why there were so many safety pins?

18. Do you remember what you were wearing? *And* Do you remember what colour sweater I was wearing?

19. Do you remember what the lunch room looked like? *And* Do you remember any things or objects that were in the lunch room?

20. Do you remember watching a video?
   *If yes,* Can you describe the video for me (i.e., name of it, favourite part, etc.)?
Appendix M

*Non-Parametric Mann-Whitney Tests for Group Differences in AM Performance in Study III*

<table>
<thead>
<tr>
<th>Variable</th>
<th>Mann-Whitney test statistic (U)</th>
<th>z-score</th>
<th>p-value</th>
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<tbody>
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<td><strong>Recall + Specific Probe Condition:</strong></td>
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<td></td>
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<td>Inaccurate event details</td>
<td>502.00</td>
<td>-0.56</td>
<td>.576</td>
</tr>
<tr>
<td>Inaccurate place details</td>
<td>505.50</td>
<td>-0.54</td>
<td>.590</td>
</tr>
<tr>
<td>Inaccurate time details</td>
<td>545.00</td>
<td>-0.01</td>
<td>.990</td>
</tr>
<tr>
<td>Inaccurate perceptual details</td>
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<td>-0.70</td>
<td>.481</td>
</tr>
<tr>
<td>Total accurate details</td>
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<td>.004</td>
</tr>
<tr>
<td>Accurate event details</td>
<td>385.50</td>
<td>-2.03</td>
<td>.042</td>
</tr>
<tr>
<td>Accurate place details</td>
<td>383.00</td>
<td>-2.08</td>
<td>.037</td>
</tr>
<tr>
<td>Accurate time details</td>
<td>427.50</td>
<td>-1.54</td>
<td>.123</td>
</tr>
<tr>
<td>Accurate perceptual details</td>
<td>346.50</td>
<td>-2.52</td>
<td>.012</td>
</tr>
<tr>
<td>Accurate visual details</td>
<td>330.50</td>
<td>-2.73</td>
<td>.006</td>
</tr>
<tr>
<td>Accurate non-visual details</td>
<td>449.50</td>
<td>-1.23</td>
<td>.220</td>
</tr>
<tr>
<td>Proportion Accuracy Score</td>
<td>346.50</td>
<td>-2.52</td>
<td>.012</td>
</tr>
</tbody>
</table>

Note: Variables in *italics* represent those that were significantly non-normal on the Kolmogorov-Smirnov test. These results are similar to those reported in Study II using parametric tests.
Appendix N

Personal Semantic Questionnaire for Study IV

1) What is your first name? ________________________________________________

2) What is your middle name? ____________________________________________

3) What is your last name? ______________________________________________

4) How old are you? _____________________________________________________

5) What grade are you in? ________________________________________________

6) What is your eye colour? ______________________________________________

7) What colour would you say your hair was? ________________________________

8) Are you left or right handed? __________________________________________

9) Do you have any allergies? If yes, what are they? _________________________

10) Do you have Asthma? _________________________________________________

11) In what city were you born? ___________________________________________

12) Where you born in a hospital? _________________________________________

13) What city do you live in now? _________________________________________

14) Do you live with both your parents? ____________________________________

15) What street do you live on? __________________________________________

16) What is your house number? __________________________________________

17) Do you live in a house or an apartment? _________________________________

18) What is the area code of your phone number? ____________________________

19) Have you ever moved before? _________________________________________

20) What is your birthday (including the year you were born)? ________________

21) What are your parents’ first names? ____________________________________

22) What is your dad’s job? ________________________________________________

23) What is your mom’s job? ______________________________________________

24) How many brothers and/or sisters do you have? __________________________

25) Are you the oldest, middle, or youngest child? ___________________________

26) How many cousins do you have? ______________________________________

27) What are the first names of one of your Aunts and Uncles? _________________

28) Do you know any of your grandparents’ first names? ______________________

29) What cities do your grandparents live in? ________________________________

30) Have you ever had a pet? If yes, what kind of pet(s) do you have and what is/are their name(s)? ________________________________

31) Name three of your closest friends: _____________________________________

32) What is your elementary school called? _________________________________

33) What city is your school in? __________________________________________

34) Do you know what street your school is on? _____________________________

35) How do you get to school every day? __________________________________

36) What is your favorite subject in school? _________________________________

37) What is your least favorite subject in school? _____________________________

38) What grade are you in or going into? __________________________________

39) Name two teachers you’ve had in the past. ______________________________

40) Do you have to wear a uniform to school? ______________________________

41) Do you play a musical instrument? If yes, which one? ____________________

42) What is the colour of your family car(s)? ________________________________

43) What is the colour of your room at home? _______________________________
44) What is your favorite TV show? ________________________________________
45) What was the best movie you saw this year? ______________________________________
46) Which Disney movies have you seen? ________________________________________
47) Have you read any of the Harry Potter books? ______________________________________
48) What is your favorite type of food? ________________________________________
49) What do you normally eat for breakfast? ______________________________________
50) Have you ever gone skiing before? ________________________________________
51) Have you ever gone snowshoeing before? ______________________________________
52) Have you ever played a sport? If yes, which one? ______________________________________
53) Which Canadian provinces have you been to? ______________________________________
54) Have you ever swam in Lake Ontario? ________________________________________
55) Have you ever been outside of Canada? If so, to which countries? ______________________________________
56) Are you afraid of spiders? ________________________________________
57) Are you afraid of heights? ________________________________________
58) Do you have a bicycle? ________________________________________
59) Do you have rollerblades? ________________________________________
60) Have you ever played the Wii? ________________________________________
61) Do you have a favorite video game? ________________________________________
62) Do you know how to speak another language besides English? If yes, which one(s)? ________________________________________
63) Have you ever been on a plane? ________________________________________
64) Have you ever been on the GO train? ________________________________________
65) Have you ever gone bungee jumping? ________________________________________
66) Have you ever gone sky diving? ________________________________________
67) What is your favorite kind of chocolate bar? ________________________________________
68) Have you ever broken a bone? ________________________________________
69) What are some of your hobbies? ________________________________________
70) What is your postal code? ________________________________________
71) Do you have your own email address? ________________________________________
72) Do you belong to any clubs? ________________________________________
73) Have you ever gone to see a hockey game? ________________________________________
74) Are there computers at your school? ________________________________________
75) Have you ever gone fishing? ________________________________________
Appendix O

Functional MRI Sentence Verification Task for Study IV

- Instructions
- Fixation (20 seconds)
- Fixation (2 seconds)
- Cue for PE condition (1 second)
- Fixation (2 seconds)
- PE condition (Four 6-second questions)
  - Was your brother at your party?
  - Was your party on a Friday?
  - Did you have chocolate cake?
  - Did you watch the movie ‘Up’?
- Fixation (2 seconds)
- Cue for PS condition (1 second)
- Fixation (2 seconds)
- PS condition (Six 4-second questions)
  - Is your name Amy?
  - Are you 9 years old?
  - Are you left-handed?
- Fixation (2 seconds)
- Cue for GS condition (1 second)
- Fixation (2 seconds)
- GS condition (Six 4-second questions)
  - Are stop signs red?
  - Is a guitar a musical instrument?
  - Do cars go faster than airplanes?
Appendix P

**General Semantic (GS) Questions Adapted from Rekkas and Constable (2005) and Used in the fMRI Sentence Verification Task for Study IV**

<table>
<thead>
<tr>
<th>Question</th>
<th>Question</th>
<th>Question</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Is a guitar a musical instrument?</td>
<td>46. <em>Is the letter ‘E’ a consonant?</em></td>
<td>91. Is Saturn a planet?</td>
</tr>
<tr>
<td>3. <em>Is Halloween in March?</em></td>
<td>48. Are forks used for eating?</td>
<td>93. Are carrots orange?</td>
</tr>
<tr>
<td>4. <em>Do cats have twenty legs?</em></td>
<td>49. <em>Is a bathtub a musical instrument?</em></td>
<td>94. Is ice frozen water?</td>
</tr>
<tr>
<td>5. Is milk something people drink?</td>
<td>50. Is coffee a type of drink?</td>
<td>95. Are stop signs red?</td>
</tr>
<tr>
<td>7. Is Canada the name of a country?</td>
<td>52. Are dogs common house pets?</td>
<td></td>
</tr>
<tr>
<td>8. Is ice cream a type of dessert?</td>
<td>53. <em>Is peanut butter a type of drink?</em></td>
<td></td>
</tr>
<tr>
<td>9. Do humans have two ears?</td>
<td>54. Are elephants large animals?</td>
<td></td>
</tr>
<tr>
<td>10. Is Monday a day of the week?</td>
<td>55. Is Ontario the name of a province?</td>
<td></td>
</tr>
<tr>
<td>11. <em>Is a rectangle a type of vegetable?</em></td>
<td>56. Is pumpkin pie a type of dessert?</td>
<td></td>
</tr>
<tr>
<td>12. Are there seven days in one week?</td>
<td>57. Do humans need oxygen to breathe?</td>
<td></td>
</tr>
<tr>
<td>13. Are boots worn on the feet?</td>
<td>58. <em>Are lawn mowers used to tell time?</em></td>
<td></td>
</tr>
<tr>
<td>14. <em>Is honey made from broccoli?</em></td>
<td>59. Are apples a type of fruit?</td>
<td></td>
</tr>
<tr>
<td>15. Are toasters found in kitchens?</td>
<td>60. Do teachers work in schools?</td>
<td></td>
</tr>
<tr>
<td>16. Is the letter ‘A’ a vowel?</td>
<td>61. Is rock and roll a style of music?</td>
<td></td>
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<tr>
<td>17. Do libraries contain books?</td>
<td>62. Is March a month of the year?</td>
<td></td>
</tr>
<tr>
<td>18. <em>Are computers made of wood?</em></td>
<td>63. Are dishwashers found in kitchens?</td>
<td></td>
</tr>
<tr>
<td>19. Are trucks a type of vehicle?</td>
<td>64. *Is a picture frame a type of vehicle?</td>
<td></td>
</tr>
<tr>
<td>20. <em>Do cars go faster than airplanes?</em></td>
<td>65. <em>Are rabbits found in the ocean?</em></td>
<td></td>
</tr>
<tr>
<td>21. Is chocolate a type of ice cream?</td>
<td>66. Is hockey a team sport?</td>
<td></td>
</tr>
<tr>
<td>22. Is Toronto the name of a city?</td>
<td>67. *Is chicken a type of fruit?</td>
<td></td>
</tr>
<tr>
<td>23. Are fish found in the ocean?</td>
<td>68. Is Friday a day of the week?</td>
<td></td>
</tr>
<tr>
<td>24. Are clocks used to tell time?</td>
<td>69. Are sandals worn on the feet?</td>
<td></td>
</tr>
<tr>
<td>25. Is a piano a musical instrument?</td>
<td>70. *Is the letter ‘J’ a vowel?</td>
<td></td>
</tr>
<tr>
<td>26. Are pens used for writing?</td>
<td>71. Are dolphins found in the ocean?</td>
<td></td>
</tr>
<tr>
<td>27. *Is New Year’s Eve in May?</td>
<td>72. Is a bed a type of furniture?</td>
<td></td>
</tr>
<tr>
<td>28. Are whales found in oceans?</td>
<td>73. Is a trumpet a musical instrument?</td>
<td></td>
</tr>
<tr>
<td>29. Is hot chocolate a type of drink?</td>
<td>74. *Is snow usually green?</td>
<td></td>
</tr>
<tr>
<td>30. Is purple the name of a colour?</td>
<td>75. Is Thanksgiving a holiday in autumn?</td>
<td></td>
</tr>
<tr>
<td>31. <em>Is Paris the capital of Canada?</em></td>
<td>76. Does a conductor work on a train?</td>
<td></td>
</tr>
<tr>
<td>32. <em>Is Lasagna a type of dessert?</em></td>
<td>77. Is iced tea something people drink?</td>
<td></td>
</tr>
<tr>
<td>33. Do Doctors work in hospitals?</td>
<td>78. Are owls a type of bird?</td>
<td></td>
</tr>
<tr>
<td>34. Is Sunday a day of the week?</td>
<td>79. Is China the name of a country?</td>
<td></td>
</tr>
<tr>
<td>35. Is pineapple a type of fruit?</td>
<td>80. Is chocolate cake a type of dessert?</td>
<td></td>
</tr>
<tr>
<td>36. Is pepper the name of a spice?</td>
<td>81. Do humans have two eyes?</td>
<td></td>
</tr>
<tr>
<td>37. Are ice skates worn on the feet?</td>
<td>82. <em>Are tigers common house pets?</em></td>
<td></td>
</tr>
<tr>
<td>38. Is soccer a type of sport?</td>
<td>83. *Are strawberries a type of vegetable?</td>
<td></td>
</tr>
<tr>
<td>39. <em>Are bathtubs found in kitchens?</em></td>
<td>84. Is basketball a type of sport?</td>
<td></td>
</tr>
<tr>
<td>40. Is pink the name of a colour?</td>
<td>85. *Are gloves worn on the feet?</td>
<td></td>
</tr>
<tr>
<td>41. Is the letter ‘K’ a consonant?</td>
<td>86. Is July a month of the year?</td>
<td></td>
</tr>
<tr>
<td>42. Is chalk used for writing?</td>
<td>87. Is Quebec a province in Canada?</td>
<td></td>
</tr>
<tr>
<td>43. Are minivans a type of vehicle?</td>
<td>88. Does it usually snow during the winter?</td>
<td></td>
</tr>
<tr>
<td>44. <em>Is a mouse larger than a horse?</em></td>
<td>89. Is a motorcycle a type of vehicle?</td>
<td></td>
</tr>
<tr>
<td>45. Is Vanilla a type of ice cream?</td>
<td>90. Can tables be made out of wood?</td>
<td></td>
</tr>
</tbody>
</table>

Note: questions in italics are false
Appendix Q

Instructions for the fMRI Task for Study IV

For this study you are going to answer some yes or no questions about the five events you told me about the last time you were here. For example, last time you told me about (memory 1 title), (memory 2 title), (the lunch break from the last time you were here; i.e., the staged event), (memory 3 title), and (memory 4 title). Do you remember each of these events? Okay, first for this practice session, you’re going to answer questions about (memory title). You’re going to see an instruction page before the questions start to let you know which event you will be asked about. Before these types of questions appear on the screen, you will see this calendar symbol to let you know that the next couple of questions will be about an event, in this case (memory 1 title). Each of these questions will stay on the screen for 6 seconds and you’ll need to answer yes or no before the 6 seconds is up, so try not to take too long to respond. To answer yes, use your (pointer finger) with this button. To answer no, use your (middle finger) with this button. If you don’t know the answer, just make your best guess as quickly as you can. I also want you to try your best to think about the event while you’re answering the questions, so try to picture it in your head and remember as many details as you can until the next question comes on the screen.

There are also two other categories of yes or no questions that you are going to answer during this task. One category includes questions about you, like your name and hobbies. When you see this picture of a (boy/girl) you’ll know that the next couple of questions will be about yourself. These questions will only be shown for 4 seconds so you’ll have to respond a little faster to these ones, and respond the same way, pressing this button for yes, and this button for no. Finally, the last category includes questions about general knowledge or facts, like ‘Is yellow a colour?’ and the symbol for this category will be this globe. These questions are also only shown for 4 seconds. So, overall there are going to be questions about one of the event, questions about you, and then general knowledge questions. Okay so let’s practice...

When you’re in the scanner, there are going to be more questions from each of these three categories so it will take a little longer. You will do this task four times, the first one will be about (memory title), the next about (the lunch break from the last time you were here; i.e., the staged event), the third about (memory title), and the last one about (memory title). Each time, you will be shown an instruction page that will tell you which event you are going to be answering questions about. Once you’ve gone through all three categories of questions a few times, you’ll start again with a new event. And this will happen four times in total. Do you have any questions?