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## Hippocampal Volumetry And Episodic Memory In Preterm Born Children

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**HIPPOCAMPAL VOLUMETRY AND EPISODIC MEMORY IN PRETERM BORN CHILDREN**

by

**DANA M. MCCALL**

**DISSERTATION**

Submitted to the Graduate School

of Wayne State University,

Detroit, Michigan

in partial fulfillment of the requirements

for the degree of

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Approved By:

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## CHAPTER 1 INTRODUCTION

Various factors impact development of the brain and cognition and it is important to understand how these factors lead to deviations from typical development of brain-behavior relationships. The main factor of interest for this study is premature birth. Premature birth is relatively common (CDC, 2016; World Health Organization, 2016) and the incidence is increasing (de Kieviet, Zoetebier, van Elburg, Vermeulen, & Oosterlaan, 2012). Premature birth has been linked to several alterations in brain (de Kieviet et al., 2012) and cognitive development (Aarnoudse-Moens et al., 2009; Allotey et al., 2017; Bhutta et al., 2003). Specifically, the hippocampus (Hc) volume is known to be significantly smaller in preterm born, compared to term born, individuals as early as term-equivalent age (40 weeks gestational age; i.e. Isaacs et al., 2000). Additionally, preterm born individuals display deficits in episodic memory, which may be related to the aforementioned decreased Hc volume. A second factor that impacts Hc development is Socioeconomic status (SES). Low SES is known to negatively impact Hc volume (Alfarez, Joels, & Krugers, 2003; Carrion, Weems, & Reiss, 2007; Hanson et al., 2015; McEwen, 1999; & Mirescu & Gould, 2006) and cognition (Farah et al., 2006; Hackman & Farah, 2009; Herrmann, 1997; Jednorog et al., 2012; Noble, McCandliss, & Farah, 2007; Noble, Norman, & Farah, 2005).

The current body of literature indicates there are inconsistencies in the specifics of the effects of premature birth and SES on Hc volume and episodic memory. Furthermore, there is minimal research on the effects of these factors on the subregion and subfield volumes of the Hc, especially in children under the age of 7. The aims of this study were motivated and guided by a review of the current literature, which included a new meta-analysis (described below) on the effects of premature birth on the Hc.

In addition to the meta-analysis, I investigated (a) the volume of the total Hc, subregions of the Hc, and subfields of the Hc, across gestational age, birth weight, and SES; (b) the construct validity of tasks that are thought to measure episodic memory and whether performance on these tasks are affected by gestational age, birth weight, or SES; and (c) the relationship between Hc volume and memory performance in young children across gestational age, birth weight, and SES. To accomplish these aims, this study assessed children in the Metro Detroit area with both cognitive measures and magnetic resonance imaging (MRI).

### **Volume of the Hc and Memory**

The Hc is a complex structure composed of subregions and subfields for which animal, postmortem studies, and limited evidence from human in-vivo studies suggest complex trajectories of change over development. For example, the Hc displays complex developmental differences in structure and function in a cross-sectional sample (e.g. Daugherty, Bender, Raz, N., & Ofen, 2016). Some evidence suggests that for total Hc volume there is relative stability from 4 years of age to adulthood (Gogtay et al., 2006); however, others suggest that the Hc continues to develop until later in life (Omizzolo et al., 2013). In large part, whether differences in structural measures of the Hc are observed or not depends on the specific structural measure used, with age differences being typically observed in cases that use regional Hc measures, rather than its total volume (Daugherty, Flinn, Ofen, 2017).

It is thought that because the Hc is positioned where the visual, auditory, and spatial processing streams converge, it is particularly involved in the execution of cognitive processes aimed at binding together pieces of information such as an object and location in space (Nosarti & Froudus-Walsh, 2016; Rolls, 2013). Episodic memory refers to the ability to remember past events and experiences. It requires the encoding, retention, and retrieval of relational information, such

as information about a specific time and references a specific person, place, or event (Eichenbaum, 2001; Ngo, Newcombe, & Olson, 2017; Tulving, 2002). In its core, episodic memory is considered to be akin to the process by which one can accomplish a mental time travel to a specific time and place in which certain experience has occurred (Tulving, 1998). A central aspect of episodic memory is the specificity of details defining past experiences, and the ability to make correct associations between specific details that belong to the same event. Thus, successful representation in episodic memory often requires association of two or more pieces of detailed information (Allen & Fortin, 2013).

A large body of evidence supports the idea that episodic memory is not fully developed until adolescence (Bauer et al., 2013; Tulving, 2002) as opposed to memory for individual items that develops early (Ngo et al., 2017; Riggins, 2014; Sluzenski, Newcombe, & Ottinger, 2004; Sluzenski, Newcombe & Kovacs, 2006). Perhaps the most protracted development is for cases when a high level of similarity exists among specific details such that successful episodic memories not only requires the association of different aspects of an experience but the distinction between separate events and between the specific details of the events (Ngo et al., 2017).

Episodic memory can be, and traditionally has been, assessed by performance on a variety of tasks. Examples of tasks that have been used to measure episodic memory include a word-list recall task (e.g. Omizzolo et al., 2013), a source recall task that requires recall of both a fact and the person that provided the fact (e.g. Rajan & Bell, 2014), a picture recall task that requires recall of the content and location of a series of pictures (Bauer et al., 2013), and a pair recall task that requires recall of both components of an associated pair (e.g. Salvan et al., 2014; Daugherty & Ofen, 2015). However, this memory system is not yet fully understood, and it is not clear which

tasks provide the most accurate assessment of the various cognitive processes needed for episodic memory, especially in young children (Tulving, 2002).

In reviewing the literature one can appreciate that there are inconsistencies in relationship between Hc volume and episodic memory performance across development. Specifically, in one meta-analysis it was noted that children and adolescents (ages 7 years and up) display a negative correlation between Hc volume and memory performance; whereas adults display a positive correlation (Van Petten, 2004). Additionally, the volume-performance relationship appears to not apply to all episodic memory tasks as Hc volume is related to some measures of episodic memory performance but not others (Brunnemann et al., 2013). This variability of results may be due to suboptimal measures, such as overall Hc volume instead of subcomponent volume or single task performance instead of a composite score. Alternatively, this variability may be due to some measure of individual differences that was not captured in the studies. In addition to individual differences in typical development, there are several factors that can contribute to atypical development of the Hc and memory. The factors that are of interest in this study are premature birth and SES.

### **Premature Birth, Volume of the Hc, and Memory**

Premature birth (born before 37 weeks gestational age) occurs in more than 1 in every 10 births annually and this rate appears to be rising world-wide (CDC, 2016; World Health Organization, 2016). Additionally, improvements in medical practices have improved survival rates following premature birth (de Kieviet et al., 2012). Thus, it is important to investigate the outcomes following premature birth. Premature birth is of particular interest when investigating the Hc and memory performance, as some of the complications that frequently accompany premature birth are known to negatively impact the Hc. For example, hypoxic-ischemic events, or

reduced oxygen and blood flow to the brain, (Abernethy, Palaniappan, & Cooke, 2002; Cooper et al., 2015; Schmidt-Kastner, 2015; Schmidt-Kastner, & Freund, 1991; Thompson et al., 2013), stress hormones (McEwen, 2001), and under-nutrition (Isaacs et al., 2000) are known to be particularly harmful to the Hc.

There is evidence that preterm born individuals display smaller Hc volume at term-equivalent age (Brunnemann et al., 2013; Isaacs et al., 2000; Omizzolo et al., 2013), at school age (Brunnemann et al., 2013; Thompson et al., 2014), as adolescents (Isaacs et al., 2000; Nosarti et al., 2002), and as adults (Aanes, Bjuland, Skranes, & Lohaugen, 2015; Molnar & Keri, 2014). This reduction in Hc volume compared to term born controls was also observed in children with a small risk for negative outcomes (Brunnemann et al., 2013). However, there is some evidence to suggest that the full extent of Hc volume reductions in preterm born individuals may not be observed until later in childhood (Omizzolo et al., 2013). Additionally, a 2012 meta-analysis reported total brain volume is significantly less in preterm born individuals (de Kieviet et al., 2012). However, the significance of other anatomical differences, such as Hc volume, between these groups depends on the experimental design of the research – a whole-brain approach verses a region-specific approach (de Kieviet et al., 2012). Therefore, the reduced Hc volume observed in preterm born individuals compared to term born may or may not hold true when Hc volume is corrected for total brain volume (de Kieviet et al., 2012; Fraello et al., 2011; Omizzolo et al., 2013).

Premature birth is also associated with deficits in overall intellectual functioning, academic achievement, language, memory, and executive function (Aarnoudse-Moens et al., 2009; Allotey et al., 2017; Bhutta et al., 2003; de Kieviet et al., 2012), even in early childhood. Furthermore, the degree of prematurity is related to these deficits such that those with lower gestational age and smaller birth weight display more significant deficits (Aarnoudse-Moens et al., 2009; Allotey et

al., 2017; Bhutta et al., 2003). The specifics of the memory deficits that preterm born individuals experience compared to term born are not fully understood. For example, there is some evidence to suggest that only preterm born children with severe medical complications at birth display deficits in memory performance, even if they display deficits in intellectual functioning (Briscoe & Gathercole, 2001; Brunnemann et al., 2013). Additionally, there is evidence to suggest that preterm born children display both visual (Omizzolo et al., 2013; Thompson et al., 2013) and verbal memory (Thompson et al., 2013) impairments compared to term born controls. However, there is also evidence to suggest that verbal memory is intact following premature birth (Omizzolo et al., 2013). Overall, it appears that premature birth, and thus gestational age and/or birth weight, is related to deficits in memory and cognition but the specifics of these deficits are not clear at this time.

In one meta-analysis by de Kieviet and colleagues (2012) the authors identified decreased brain volume in preterm, compared to term, born individuals that was related to cognitive deficits (de Kieviet et al., 2012); however, that analysis only included four studies that had included measures of Hc volumes. Some findings suggest that reduced Hc volume is correlated with impairments in episodic memory performance in preterm born children as early as age 7 (Isaacs et al., 2000), but others suggest that deficits in memory performance following injury to the Hc may not be apparent until later in childhood (Cooper et al., 2015; Cordova-Palomera et al., 2015; de Haan, Mishkin, Baldeweg, & Vargha-Khadem, 2006; de Haan, Wyatt et al., 2006; Gadian et al., 2000; Isaacs et al., 2003; Maneru et al., 2003; Raman, Georgieff & Rao, 2006; Vargha-Khadem et al., 2003). Interestingly, there is evidence that Hc volume at term-equivalent age relates to episodic memory performance at age seven (Thompson et al., 2013) but that neither Hc volume at age seven (Omizzolo et al., 2013) nor the change in Hc volume from term-equivalent age to age seven relates

to memory performance at age seven (Nosarti & Froudish-Walsh, 2016; Thompson et al., 2014). Additionally, preterm born children may display intact memory performance despite reduced Hc volumes due to alternate neuronal networks that allow other regions to compensate for the decreased Hc function (Brunnemann et al., 2013).

Overall there are several contradictory findings about the effects of premature birth on Hc volume and the volume-performance relationships between Hc and memory. Previously published meta-analyses were only able to include a few studies that investigated Hc volume in preterm born individuals and no previous meta-analysis statistically evaluated the relationship between Hc volume and cognition following preterm birth. Additionally, with neuroimaging methods gaining popularity as tools to investigate brain development, there is a growing body of work investigating the effects of preterm birth on brain development. Attempts to generate understanding of the general trends require a systematic synthesis that is kept up to date with recent publications. Therefore, to guide this project and to provide a more complete understanding of the characteristics of Hc volume and the volume-performance relationship in the preterm born population, a meta-analysis was completed.

### **Volume of Hc and Cognitive Performance in Preterm Born Individuals: A Systematic Literature Review**

**Meta-analysis methods: Selection of papers.** Original, peer-reviewed articles with the information of interest were located through PsycINFO, PubMed, and Web of Science in January 2017 and again in April 2018. The search terms were (preterm OR premature OR low birth weight) AND (hippocamp\* OR total brain volume) AND (cognition OR memory OR IQ OR intell\* OR executive function OR language). Additional literature searches including just the preterm and the brain search terms were included to ensure all applicable articles were identified. Articles were

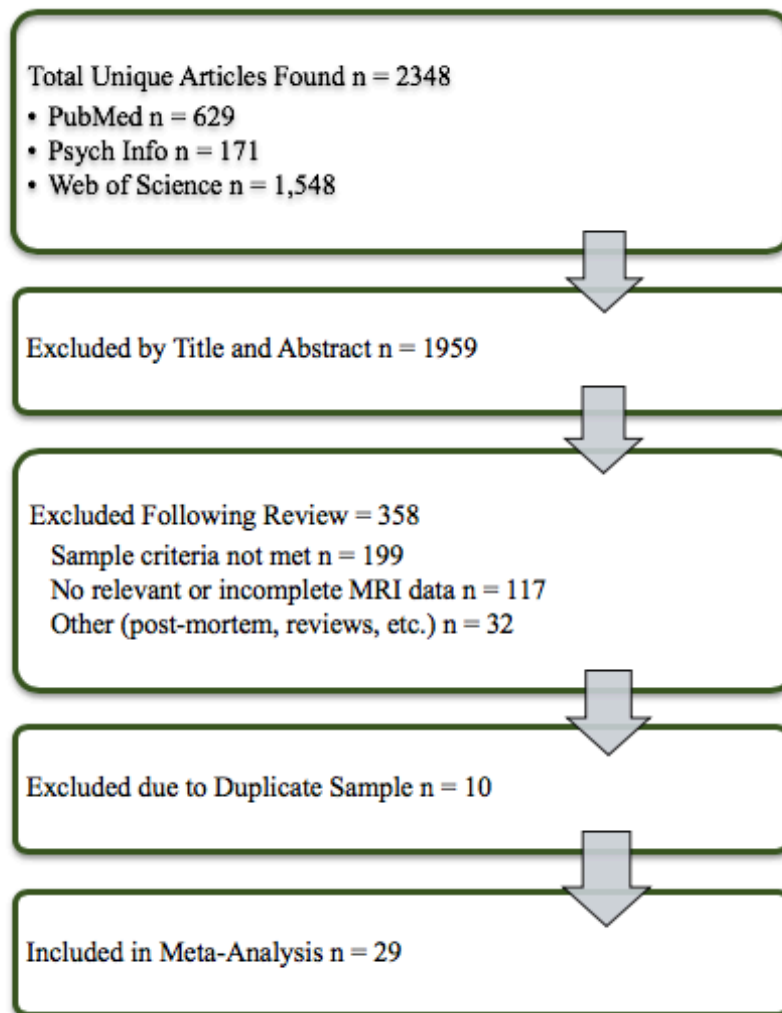


selected for inclusion if they met the following criteria: (a) included a unique (did not include the same MRI data as another study) and generalizable (i.e., not restricted to only participants who had white matter injury or a specific medical diagnosis) sample of human preterm born participants of any postnatal age; (b) used a case-control study design; (c) reported sufficient Hc volume data to complete the meta-analyses; and (d) was published in English in a peer-reviewed journal. The reference lists of the selected articles were also searched for additional articles that met the inclusion criteria. If two studies used participants from the same cohort but reported MRI data from different ages, both studies were included. If multiple studies included participants from the same population with MRI data from the same age, only the study with the most complete report of Hc data and the most relevant cognitive data was included.

The initial search located 2348 unique articles. Of these initial articles, 389 remained after an initial screening of titles and abstracts (See Figure 1). The remaining articles were further reviewed based on the inclusion criteria and evaluated for duplicate cohorts of participants. After full review, 29 articles remained for inclusion in the analyses (See Appendix A). If one cohort was scanned at multiple time points, each MRI age was coded separately, which resulted in 30 studies, with 1590 preterm participants and 1095 term-born controls, that were included in the following analyses.

**Meta-analysis methods: Coding and statistical analysis.** Due to variations in reported variables and to avoid inflating the homogeneity of the overall results by including several measures from the same study in a single analysis, several meta-analyses were conducted. Specifically, separate analyses were completed for mean differences between preterm and term born individuals in uncorrected total Hc volume, uncorrected left Hc volume, uncorrected right Hc volume, corrected total Hc volume, corrected left Hc volume, and corrected right Hc volume.

Additionally, meta-analyses were conducted on the relationship between Hc volume and cognitive performance (studies that looked intelligence and memory were combined into one analysis) for preterm born individuals only as there was insufficient reporting of this data for the term born controls.



*Figure 1.* Literature review results for meta-analysis.

The Meta-Essentials 1.1 macro for Microsoft Excel (Hak, Van Rhee, & Suurmond, 2016; Van Rhee, Suurmond, & Hak, 2015) was used for all analyses. A random effects model was used, and all effect sizes were expressed as standardized mean differences between the preterm born and term born sample (Hedges'  $g$ ; Hedges, 1981) for all analyses except for those testing the

relationship between Hc volume and cognition, which were conducted using Pearson's  $r$  as the effect size. Effect sizes were weighted by a measure of inverse variance ( $1/(SE^2 + \text{Tau}^2)$ ) where Tau is an estimation of the variance of the population effect sizes. Homogeneity of effect sizes was assessed using the  $Q$  and  $I^2$  statistics provided by the Meta-Essentials macro. If an overall effect displayed substantial heterogeneity (i.e. significant  $Q$  test or  $I^2$  approximately 50% or greater), average preterm gestational age, average preterm birth weight, and average preterm age at testing for each individual study were tested as potential moderators. For all homogenous results the potential for publication bias was evaluated by a funnel plot and tested using the failsafe  $N$  provided in the Meta-Essentials macro.

**Meta-analyses results: Volume of the Hc.** The mean difference in total uncorrected Hc volume was extracted from six studies (See Appendix A). Total uncorrected Hc volume was decreased in preterm born individuals compared to term born individuals ( $g = -0.66$ , 95%CI: -1.09 to -0.24; Figure 2). The homogeneity test was nonsignificant using the  $Q$  statistic ( $Q = 8.84$ ,  $p = .12$ ) but the  $I^2$  was small-to-medium ( $I^2 = 43.33\%$ ) so potential moderators were investigated (Borenstein, Hedges, Higgins, & Rothstein, 2009). Average preterm gestational age ( $p = .33$ ,  $R^2 = 16.19\%$ ; Figure 3A) and preterm birthweight ( $p = .27$ ,  $R^2 = 20.60\%$ ; Figure 3B) appeared to moderate the mean difference between preterm and term born individuals such that studies with lower average gestational age and lower average birth weight had larger mean differences. Average preterm age did not moderate the mean difference in uncorrected total Hc volume.

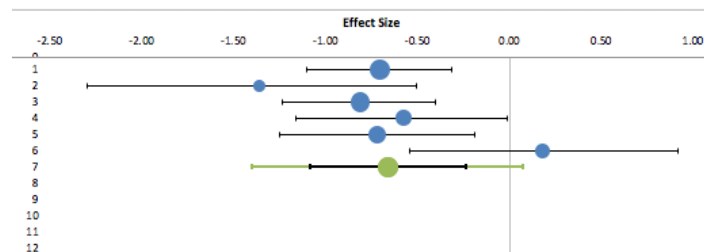


Figure 2. Mean differences for total uncorrected Hc volumes between preterm and term born.

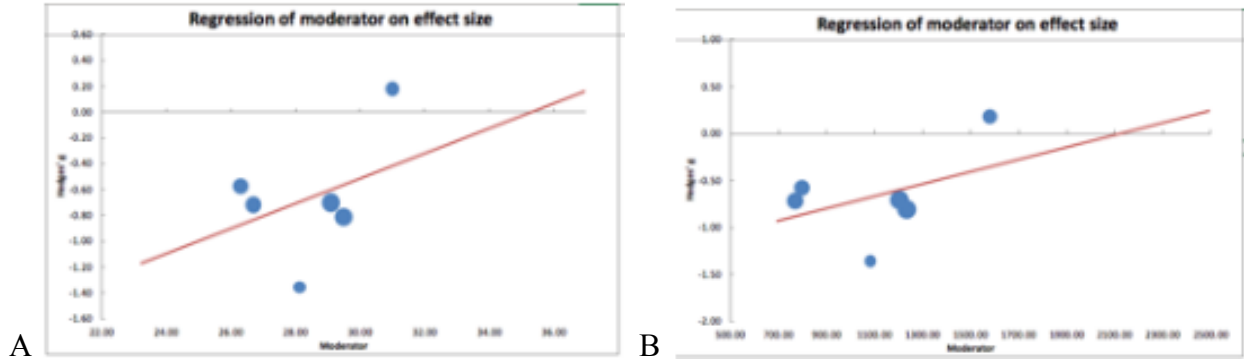


Figure 3. Moderator analysis for total uncorrected Hc volume using preterm gestational age (A) and preterm birthweight (B) as moderators.

The mean difference in left uncorrected Hc volume was extracted from 11 studies (See Appendix A). The overall effect size indicated that left uncorrected volume was smaller in preterm born individuals compared to term born ( $g = -0.60$ , 95%CI:  $-0.99$  to  $-0.22$ ; Figure 4); however, the effect sizes were heterogeneously distributed ( $Q = 40.26$ ,  $p < .01$ );  $I^2 = 75.16\%$ ) so this overall effect should be interpreted with caution. Average preterm gestational age ( $p = .08$ ,  $R^2 = 23.15\%$ ; Figure 5A) and average preterm birthweight ( $p = .27$ ,  $R^2 = 13.07\%$ ; Figure 5B) appeared to moderate the mean difference in left uncorrected Hc volume. The direction of this relationship was opposite of what was expected because studies with smaller average gestational age and birth weight reported smaller mean differences between preterm and term. Average preterm age did not appear to moderate this effect.

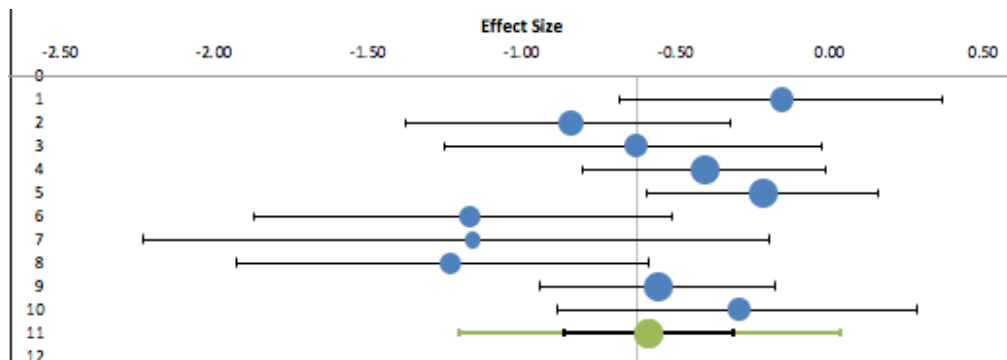


Figure 4. Mean differences for left uncorrected Hc volumes between preterm and term born.

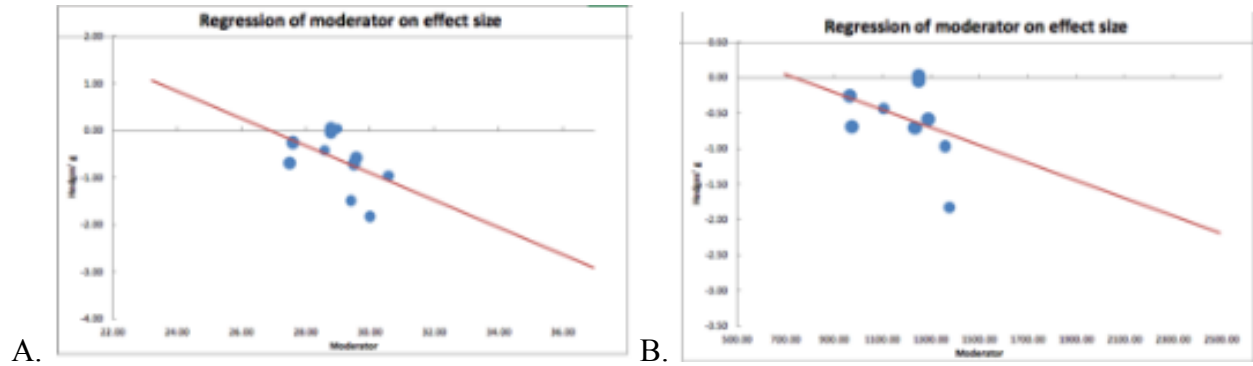


Figure 5. Moderator analysis for left uncorrected Hc volume using preterm gestational age (A) and preterm birthweight (B) as moderators.

The mean difference in right uncorrected Hc was extracted from 10 studies (See Appendix A). The overall effect size indicated that right uncorrected volume was smaller in preterm born individuals compared to term born ( $g = -0.54$ , 95%CI: -0.85 to -0.22; Figure 6); however, the effect sizes were heterogeneously distributed ( $Q = 24.19$ ,  $p < .01$ );  $I^2 = 62.80\%$ ) so this overall effect should be interpreted with caution. Average preterm gestational age was related to the mean difference in right uncorrected Hc volume such that studies with lower average gestational age had smaller effect sizes ( $p = .11$ ,  $R^2 = 23.21\%$ ; Figure 7A); similar to left uncorrected Hc volume, the direction of this relationship was unexpected. Alternatively, average preterm birthweight did not moderate the mean difference of right uncorrected Hc volume ( $p = .50$ ,  $R^2 = 6.74\%$ ; Figure 7B). Average preterm age did not appear to moderate this effect.

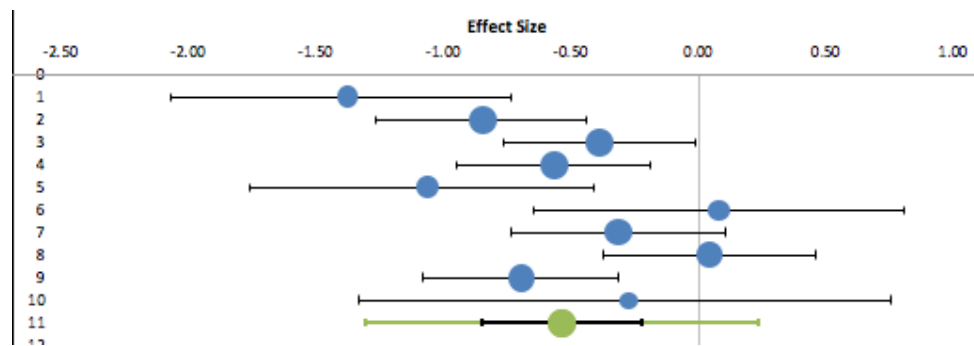


Figure 6. Mean differences for right uncorrected Hc volumes between preterm and term born.

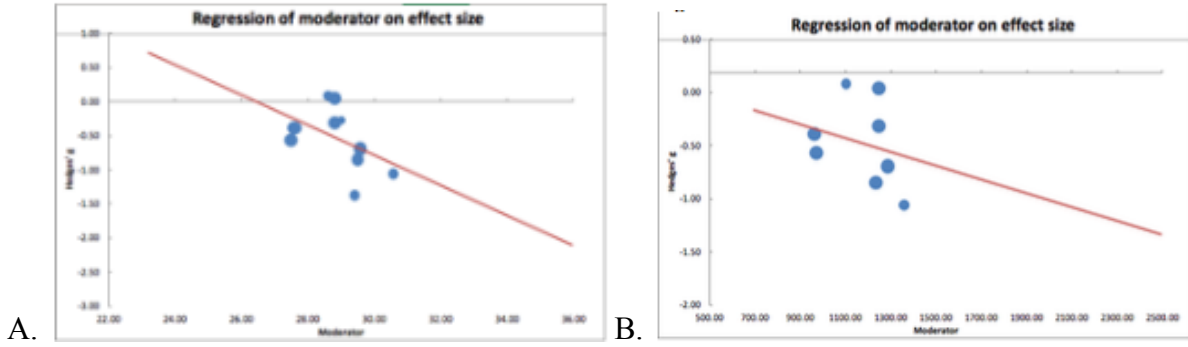


Figure 7. Moderator analysis for right uncorrected Hc volume using preterm gestational age (A) and birthweight (B) as moderators.

Total corrected Hc volume was extracted from 14 studies (See Appendix A). The overall effect size indicated that total corrected volume was also smaller in preterm born individuals compared to term born ( $g = -0.69$ , 95%CI: -1.04 to -0.33; Figure 8); however, the effect sizes were heterogeneously distributed ( $Q = 50.93$ ,  $p < .01$ );  $I^2 = 74.47\%$ ) so this overall effect should be interpreted with caution. Unlike for uncorrected total Hc volume, the overall mean difference of corrected total volume did not appear to be moderated by average gestational age ( $p = .78$ ,  $R^2 = 0.36\%$ ; Figure 9A) or average preterm birthweight ( $p = .85$ ,  $R^2 = 0.19\%$ ; Figure 9B). Again, average preterm age did not moderate the corrected total Hc volume effect.

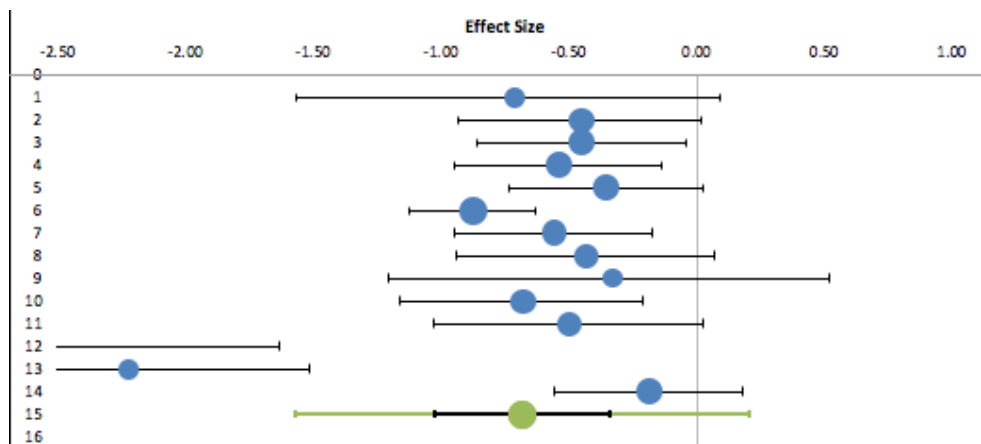


Figure 8. Mean differences for total corrected Hc volumes between preterm and term born.

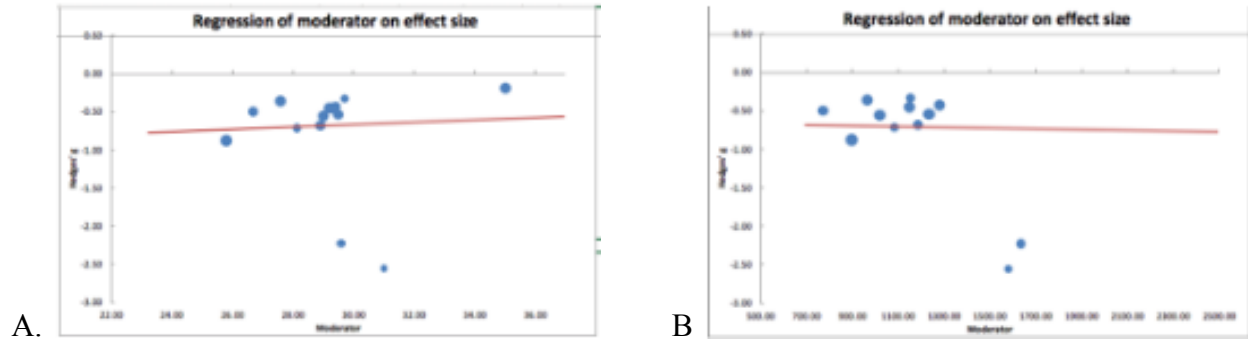


Figure 9. Moderator analysis for total corrected Hc volume using preterm gestational age (A) and preterm birthweight (B) as moderators

Left corrected Hc volume was extracted from 10 studies (See Appendix A). The overall effect size indicated that left corrected volume was also smaller in preterm born individuals compared to term born ( $g = -0.59$ , 95%CI: -0.86 to -0.31; Figure 10); however, the effect sizes were heterogeneously distributed ( $Q = 17.07$ ,  $p = .05$ );  $I^2 = 47.26\%$ ) so this overall effect should be interpreted with caution. Unlike for uncorrected left Hc volume, the overall mean difference of corrected left Hc volume was moderated only by average preterm birthweight ( $p = .11$ ,  $R^2 = 24.81\%$ ; Figure 11B). Neither average preterm gestational age ( $p = .530$ ,  $R^2 = 4.16\%$ ; Figure 11A) nor average preterm age moderated the left corrected volume.

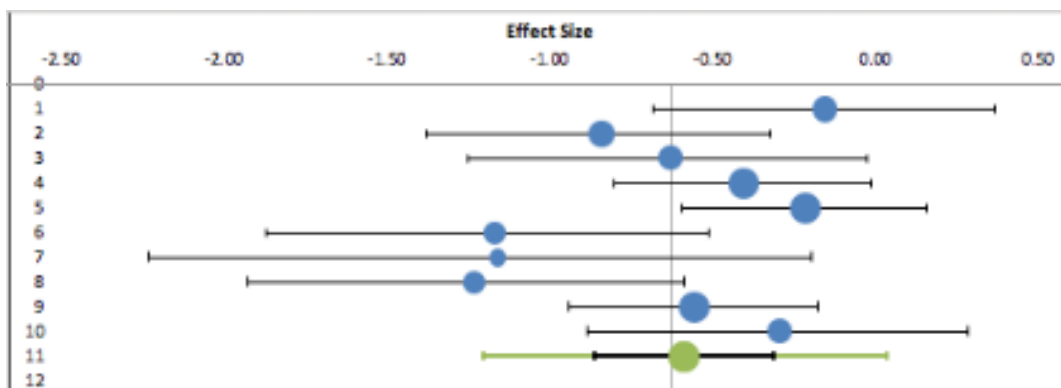


Figure 10. Mean differences for left corrected Hc volumes between preterm and term born.

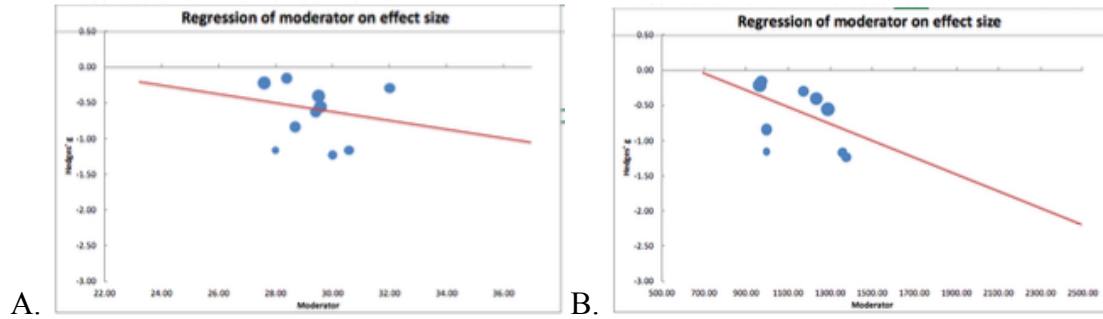


Figure 11. Moderator analysis for left corrected Hc volume using preterm gestational age (A) and preterm birthweight (B) as moderators.

Right corrected Hc volume was extracted from 10 studies (See Appendix A). The overall effect size indicated that right corrected volume was also smaller in preterm born individuals compared to term born ( $g = -0.51$ , 95%CI:  $-0.70$  to  $-0.33$ ; Figure 12). Unlike the other measures of Hc volume, the effect sizes were homogeneously distributed ( $Q = 10.50$ ,  $p = .31$ );  $I^2 = 14.28\%$ ). There is no evidence for publication bias of the right corrected Hc volume (fail-safe  $N = 171$ ).

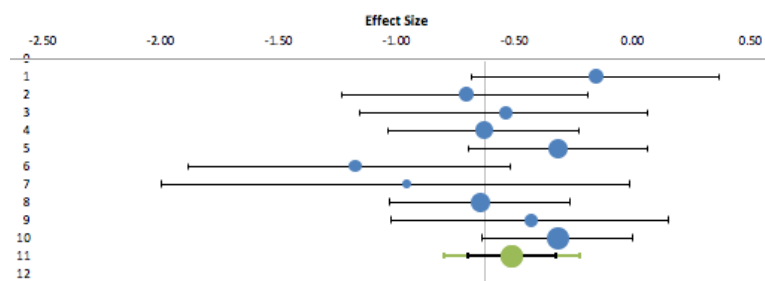


Figure 12. Mean differences for right corrected Hc volumes between preterm and term born.

**Meta-analysis results: Relationship between Hc volume and cognition.** Due to differences in reported data across studies, it was difficult to systematically evaluate the relationship between Hc volume and cognition in the same way as the mean differences in Hc volume was evaluated. Although many studies investigated Hc volume and cognition, few reported the correlation between these two variables. Additionally, the studies that reported the volume-performance correlations used different measures of Hc volume and/or cognition in their reported



correlations. Finally, most studies only reported these correlations for the preterm sample not the term controls. Below I discuss effects based on data from four studies that reported correlations between total Hc volume and intelligence in preterm born individuals and two studies that reported correlations between total Hc volume and both verbal memory and visual memory preterm born individuals.

There was a small positive correlation between Hc volume and intelligence/verbal memory in preterm born individuals ( $r = 0.28$ , 95% CI: 0.25-0.32; Figure 13A). There was a medium positive correlation between Hc volume and intelligence/visual memory in preterm born individuals ( $r = 0.32$ , 95% CI: 0.28-0.36; Figure 13B). The effect sizes were homogeneously distributed in both analyses (Verbal:  $Q = 0.49$ ,  $p = .99$ ;  $I^2 = 0.00\%$ ; Visual:  $Q = 0.73$ ,  $p = .98$ ;  $I^2 = 0.00\%$ ) and neither showed evidence for a publication bias (Verbal fail-safe  $N = 31$ ; Visual fail-safe  $N = 40$ ).

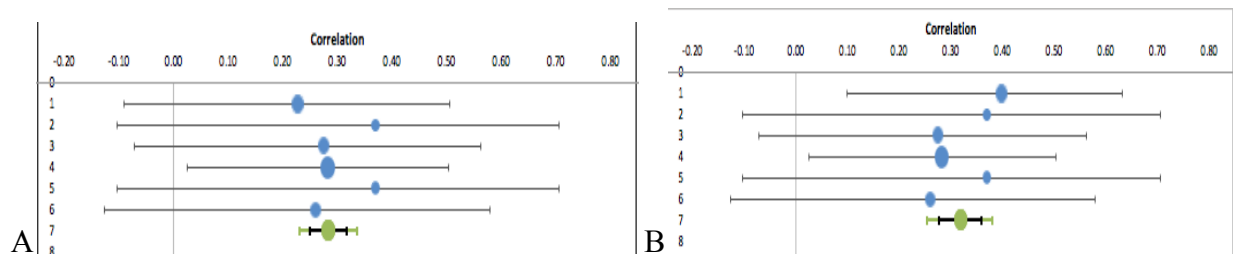


Figure 13. Meta-analysis of correlation between total Hc volume and cognition. Intelligence/verbal memory (A) and intelligence/visual memory (B).

Although the effect sizes for both correlations between total Hc volume and cognition were homogeneously distributed, an exploratory analysis of moderators was completed to search for trends that may have an impact on this correlation if there were more studies in the meta-analysis. Average age for each study displayed a potential trend in the correlation between total Hc volume and intelligence/visual memory such that younger children displayed a weaker correlation ( $p = .49$ ,  $R^2 = 65.50\%$ ; See Appendix B). This trend was not present when intelligence/verbal memory

was used ( $p = .72$ ,  $R^2 = 26.84\%$ ; See Appendix B). Neither, average gestational age nor average birthweight displayed trends of moderation for either effect.

**Meta-analysis summary.** A previous meta-analysis that included only four studies that measured Hc volume reported that premature birth may or may not result in decreased corrected Hc volume (deKieviet et al., 2012). Importantly, the meta-analysis that I completed resulted in pooled effect sizes that indicated preterm born individuals have decreased Hc volumes compared to term born when both uncorrected and correct volumes are used. Furthermore, Preterm birthweight and gestational age appear to have more of a moderating effect on the pooled mean differences of uncorrected volumes than of corrected volumes. However, these preterm variables did not fully explain the heterogeneity of effect sizes across studies. It is believed that a portion of this heterogeneity is related to using the volume of the whole Hc, which is a suboptimal measure. Analyzing the whole Hc volume is an important first step to understanding Hc function in young children, but the Hc is a not a uniform structure (Duvernoy, 2005; Scoville & Milner, 1957).

Crucially, this is the first meta-analysis to statistically demonstrate that preterm born individuals display a small to medium correlation between Hc volume and cognition. Although the correlations between Hc volume and cognition were homogeneously distributed across studies, an exploratory analysis was completed to see if there were any trends between the degree of prematurity or age and the size of the volume-performance correlation. Interestingly, this exploration suggested that there is potential that younger preterm born individuals will not display as strong of a correlation as older individuals, particularly with visual memory tasks. Similarly, although average preterm age did not account for a large portion of variance in the moderation analyses, the distribution of mean Hc volume differences in some of the analyses suggested that young children born premature may not display a significantly different Hc volume compared to

term born (See Appendix B). It is important to note that most of the studies included in the meta-analysis were cross-sectional, so this potential age effect may not represent a true developmental effect. Additionally, there were few studies that investigated early childhood between age 2-7 years. More research is needed with preterm born individuals in this age range to better understand the effect of age on the volume-performance relationship in preterm born individuals. Ultimately, this meta-analysis not only highlighted the paucity of research on Hc volume in preterm born children ages 5-7, but also provided evidence to the importance of investigating potential differentiation across the various subcomponents of the Hc.

### **Introduction for the Current Study**

The meta-analysis that I completed indicated that degree of prematurity does affect Hc volume but there is a large portion of variability that is not accounted for in these results. One important aspect that has not been systematically addressed in prior work is the possibility of these effects being specific to subcomponents of the Hc. Thus, it is important to investigate the Hc subcomponent volumes in preterm born individuals in an attempt to better account for this variability. Second, findings in this meta-analysis suggest that decreases in Hc volume and the relationship between Hc volume and memory may not be significant in young children. Importantly, there is only minimal data in the age range of 5-7 years, making it imperative to more systematically assess possible effects in this age range. Finally, within posthoc analyses of existing literature there is only limited ability to assess factors that may be important modifiers of brain and cognitive development in preterm born individuals. These factors can include the effects of environmental or genetic factors. Although the meta-analysis did not address the effects of SES on Hc volume or memory, it is important to also investigate this known factor of variability when considering the effects of premature birth. In the current study, as outlined below, I addressed many of the

limitations of the current literature that I identified with the meta-analysis. Below I elaborate on reliable ways to measure regional volumes of the Hc, assessing memory performance, and the possible contribution of premature birth and SES on Hc volume and memory. This next section sets the stage and the rationale for the study that is the primary piece of this dissertation.

**Subcomponents of the Hc and memory.** It is important to investigate the Hc subcomponent volumes in preterm born individuals in an attempt to better account for variability in whole Hc volume that was observed in the meta-analysis. There are two main methods of parsing apart the Hc into subcomponents: the subregions and subfields. The subregions vary in morphometry, or shape, along the anterior-posterior axis (Bouchard et al., 2008; Malykhin, Lebel, Coupland, Wilman, & Carter, 2010). The subregions of the Hc include the head, body, and tail (Daugherty, Yu, Flinn, Ofen, 2015). There is some evidence to suggest that Hc subregions may be sensitive to developmental changes (DeMaster et al., 2013) and may be responsible for unique memory functions (Moser & Moser, 1998). Hc head and body demonstrate a non-linear relationship with age such that adolescents have smaller volumes than children and adults but Hc tail is not significantly related to age (Daugherty et al., 2017). The anterior Hc, or the head, may be larger in young children than in adolescents (Daugherty et al., 2017) and adults (DeMaster et al., 2013) but this finding is inconsistent, as others did not find a difference in volume of the subregions across age (Lin et al., 2013).

Structural differences in the subregions are related to the variability in unique memory functions (Maquire et al., 2000; Poppenk & Moscovitch, 2011) and these relationships differ across development (DeMaster et al., 2013; Riggins, Blankenship, Mulligan, Rice, & Redcay, 2015). Better episodic memory is correlated with larger posterior (tail) volumes and smaller anterior (head) volumes in adults (Poppenk & Moscovitch, 2011) but there is evidence that these

relationships are not significant in children (DeMaster et al., 2013). Interestingly, there is a rapid change between ages 4 and 6 years old in these volume-performance relationships. Specifically, there is evidence that there is no relationship at age 4 but that head volume is positively related to memory performance at age 6. Additionally, there is evidence for more specific volume-performance relationships with the Hc subregions, but these specifics are not fully understood (Daugherty et al., 2017). For example, there is evidence to suggest that the anterior Hc is responsible for familiarity and the gist of a memory whereas the posterior regions are responsible for the detailed memories of an event (Poppenk, Evensmoen, Moscovitch, & Nadel, 2013). However, there is little evidence for significant relationships between subregional volume and item or associative memory performance in a sample of both children and adults (Daugherty et al., 2017). Even when age is a significant source of variability, there is a lot of variability in Hc subregion volumes and in these volume-performance relationships. This variability may be related to variability in the Hc subfields (Daugherty et al., 2015).

The subfields separate the Hc based on cytoarchitectonic features or cellular composition (Daugherty et al., 2017; Duvernoy, 2005). The subfields of the Hc include the cornu ammonis fields 1-3, (CA1-CA3), the dentate gyrus (DG), and the subiculum; however, there is some dispute about the reliable marcation of the individual Hc subfields (i.e. Daugherty et al., 2017; Mueller et al., 2007). For this project, the subfields that will be investigated are CA 1-2, CA3-DG, and subiculum (Bender, Daugherty, & Raz, N., 2013). When discussing subfields of the Hc, it is important to also discuss the entorhinal cortex (EC), as the EC is highly connected to the Hc and acts as an input gateway (Keresztes et al., 2017); therefore, the EC will also be investigated in this study. The subfields are thought have distinct developmental trajectories such that children (starting at age 8) have larger CA3-DG volumes than adults, CA1-2 develops non-linearly such

that adolescents have smaller volumes than children and adults, and subiculum is not significantly related to age (Daugherty et al., 2017). The subfields of the Hc are thought to be differentially related to episodic memory performance. Associative or relational memory is thought to rely on CA3-DG (Ngo et al., 2017; Norman & O'Reilly, 2003). There is some evidence that larger volumes in children and adolescents (ages 8-14) are correlated with better associative memory (Lee et al., 2014); however, there is also evidence that smaller CA3-DG volumes account for improvements in associative memory recognition (Daugherty et al., 2017).

**Measuring episodic memory in children.** Episodic memory, which requires memory for associations, is measured in many ways, but it is still unclear which tasks are best to measure development of episodic memory. Others have shown that using a composite or factor score to represent overall performance can be more applicable than individual task performance (Schmiedek, Lovden, & Lindenberger, 2014); however, it is essential that good construct validity be confirmed prior to using this factor score to represent the construct of interest. A construct, such as episodic memory, is defined as the set of cognitive processes that comprise that system (Schmiedek et al., 2014). These processes are investigated by measuring individuals' performance on a task of interest, but no one task is process-pure, or able to measure the cognitive process of interest without also measuring other processes (Schmiedek et al., 2014). Therefore, in order to more accurately measure the construct of interest, it is important to measure performance with several tasks that are thought to measure processes within the given construct. It is also important to verify that the individual performances on these various tasks correlate with each other to confirm that each task is actually measuring the construct of interest (Schmiedek et al., 2014).

If the individual performances on the different tasks do correlate with each other, there is evidence for strong construct validity, or evidence that the tasks are actually measuring what they

are intended to measure. If these performances do not correlate with each other, then the tasks may not be measuring the construct of interest or performance may be influenced more by task- or paradigm-specific variance or measurement error than by the individual differences in the cognitive processes of interest (Schmiedek et al., 2014). Crucially, Schmiedek et al. (2014) explains that one can pars apart the different types of variance in performance if the tasks are compared to other tasks that use different paradigms and content and the data is analyzed using a factor analysis. If these two criteria are met, the latent factors that are established represent only the shared variance between tasks and do not include the task-specific or paradigm-specific variance (Schmiedek et al., 2014).

Factor analysis can be used to generate a generalizable model that can be applied to individual performances across a diverse sample (Halai, Woollams, & Lambon Ralph, 2017). Additionally, a factor score can be more sensitive to change than an individual score (Yesavage et al., 2016) and less dominated by task- or paradigm specific variance (Schmiedek et al., 2014). Although factor analysis may decrease the task- and paradigm-specific variance, it does not eliminate error variance and the resulting factors, especially the first factor of the analysis, will be as error-prone as the individual tasks analyzed and can only be as reliable as the individual tasks (Raykov, Marcoulides, & Li, 2016). Therefore, it is important to only use reliable tasks when assessing for construct validity using factor analysis. In this study, I will attempt to use factor analysis to create a more reliable composite score for episodic memory. This more reliable score will be an important piece of understanding the effects of premature birth on memory and the relationship between Hc volume and memory.

**Premature birth, subcomponents of the Hc, and memory.** Little is known about Hc subregion and subfield volumes in young children who are typically developing and even less is

known about these subcomponents in preterm born individuals. Premature birth is thought to differentially impact the Hc subregions and subfields but the studies that have been completed thus far have used suboptimal measures (i.e., voxel-based Morphometry and shape analysis). Preterm born adolescents have smaller posterior Hc than their term born counterparts (Gimenez et al., 2004). Additionally, when Hc shape is considered, preterm born infants have straighter Hc with areas of expansion on lateral aspects near Hc head and tail and areas of contraction on the medial aspects near head and tail (Thompson et al., 2013). At age seven, preterm born individuals still display variations in Hc shape compared to term born individuals, but the differences were mostly in the right hemisphere near Hc head and body; however, there was little evidence that the change in shape from infancy to age seven was different for preterm born compared to term born children (Thompson et al., 2014).

In terms of the volume-performance relationship, a smaller posterior Hc volume of preterm born, compared to term born, adolescents accounted for decreased verbal learning performance (Gimenez et al., 2004). Beyond this finding, there is minimal literature on the effects of premature birth on the relationship between Hc subregion volume and memory. Nevertheless, given what is known about the impact of premature birth on the Hc, it is expected that degree of prematurity will account for some of the variability in Hc subregions. However, these birth characteristics are not expected to account for all individual differences in subregions, as some of this variability is thought to be due to individual differences in Hc subfields (Daugherty et al., 2017).

Preterm born children, particularly those born before 34 weeks gestational age, may be at higher risk for developmental differences in the Hc subfields, as the Hc cytoarchitecture is not fully formed until 34 weeks gestational age (Arnold & Trojanowski, 1996). As for variability in Hc subfields, it is likely that preterm born participants will have decreased CA1-2 volume



compared to term born participants, as these regions are particularly vulnerable to hypoxemia and ischemia (Shing et al., 2011). In a study of shape analysis, there was no significant difference in overall Hc volume between preterm and term born adolescents but there were significant alterations in shape of CA1-2 and subiculum (Cole et al., 2015). It is known that the Hc subfields are differentially vulnerable to the negative consequences of premature birth, but little is known about how premature birth effects the volume-performance relationship between subfields and episodic memory. As CA1-2 is the most vulnerable to hypoxic-ischemic events (Shing et al., 2011) that are commonly associated with premature birth, it is reasonable to expect this subfield to display differential relationships with performance across degree of prematurity.

There are several other factors that have an impact on development of the Hc and memory in addition to premature birth. The other factor that is of interest to this study is SES. SES, particularly low SES and living in poverty, is also known to impact health outcomes, cognitive development, and brain development (Cohen, Janicki-Deverts, Chen, & Matthews, 2010; Conroy, 2010; Evans, 2004; Evans & Schamberg 2009; Hackman, Farah, & Meaney, 2010; Jednorog et al., 2012; Mackey et al., 2015).

**SES, volume of the Hc, and memory.** SES during childhood can be represented with many different measures including household income, parent's education, and, parent's occupation. Living in low SES potentially means the family has less access to resources such as medical care, experiences more parental and child stress, and lives in a less stimulating or enriched environment than those with higher SES. Although measures of SES are often highly correlated, it is important to investigate the individual effects of the various measures as they may impact development differently (Brito & Noble, 2014; Duncan, 2012).

The Hc is particularly affected by both the benefits of an enriched environment (Brown et al., 2003; Miller, Colella, Mikulis, Maller, & Green, 2013) and the negative effects of low SES (Alvarez et al., 2003; Carrion et al., 2007; Hanson et al., 2015; McEwen, 1999; Mirescu & Gould, 2006). Specifically, children from lower SES households have smaller Hc volumes than children from higher SES households (Hanson, Chandra, Wolfe, & Pollak, 2011; Hanson et al., 2015; Jednorog et al., 2012; Noble et al., 2015; Yu et al., 2017). Alternatively, the enriched environment that is more readily assessable with higher SES is thought to promote increased neurogenesis in the Hc (Brown et al., 2003). Little is known about the effect of SES on the Hc subregions and subfields, but it is likely that SES will differentially affect the development of these subcomponents. Due to the continued neurogenesis into adulthood within the DG (Eriksson et al., 2000) and the protracted development (Daugherty et al., 2016), it is possible that the DG is differentially impacted by SES (Yu et al., 2017).

Low SES correlates with lower performance on several cognitive tasks including tasks of memory, executive function (Farah et al., 2006; Hackman & Farah, 2009; Herrmann, 1997; Jednorog et al., 2012; Noble et al., 2007; Noble et al., 2005) and full-scale intelligence (Lange, Froimowitz, Bigler, Lainhart, & Brain Development Cooperative, 2010). Additionally, there is evidence that SES is associated with memory performance (Noble et al., 2007). Alternatively, there is evidence that indicates when memory performance, Hc volume, and SES are considered together, memory performance is associated with Hc volume but not SES (Yu et al., 2017). Ultimately, little is known about the effects of SES on the volume-performance relationship and more research is needed to learn about these detailed relationships across both degree of prematurity and SES.

It is known that premature birth and low SES can negatively impact the development the Hc and of memory, but the specifics of these relationships are not fully understood at this time. Importantly, most of what is known about Hc volume and memory performance in children across gestational age, birth weight, and SES is based off of research with children over the age of seven years. Therefore, this study will not only attempt to clarify findings by using more detailed measurements (subcomponents of the Hc and factor scores for memory performance) but it will also broaden the understanding of these relationships in young children specifically.

### **Specific Aims and Hypotheses**

**Aim 1 – Analysis of volume of Hc, Hc subregions, and Hc subfields in children across gestational age, birth weight, and SES.** The Hc is vulnerable to the negative effects of premature birth and low SES but different components of the Hc are thought to be differentially vulnerable. The purpose of this aim is to investigate the potential relationships between Hc volume, gestational age, birth weight, and SES.

*Hypothesis 1a.* It is hypothesized that degree of prematurity will only be significantly related to Hc tail (Gimenez et al., 2004; Thompson et al., 2013) and CA1-2 (Shing et al., 2011) as they are the most vulnerable to the effects of premature birth.

*Hypothesis 1b.* It is hypothesized that SES will not only be related to total Hc volume (Yu et al., 2017) but will also be differentially related to the Hc subregions and the subfields such that the strongest effect is with the CA3-DG (Eriksson et al., 2000).

**Aim 2 – Assessment of construct validity of episodic memory tasks in children across gestational age, birth weight, and SES.** Episodic memory is a complex, multifaceted construct that requires detailed encoding, retrieval, and recall (Tulving & Markowitsch, 1998). There are many tasks that intend to measure the different aspects of episodic memory, but the construct

validity of these tasks should be confirmed. The purpose of this aim is to determine if latent constructs can be formed for associative memory and to investigate if individual differences in this factor score correlate with gestational age, birth weight, and/or SES. An additional analysis will be completed to determine if this memory factor remains stable with the addition of executive function measures. Executive function, particularly working memory, is closely related to episodic memory but they are still thought to be distinct constructs (Nosarti & Froudust-Walsh, 2016).

***Hypothesis 2a.*** It is hypothesized that there will be two separate memory factors: an item memory factor and an associative memory factor.

***Hypothesis 2b.*** It is hypothesized that degree of prematurity will be positively correlated with both factors (Aarnoudse-Moens et al., 2009; Allotey et al., 2017; Bhutta et al., 2003; de Kieviet et al., 2012).

***Hypothesis 2c.*** It is hypothesized that SES will be positively correlated with both factors (Farah et al., 2006; Hackman & Farah, 2009; Herrmann, 1997; Jednorog et al., 2012; Noble et al., 2007; Noble et al., 2005).

**Aim 3 – Assessment of relationship between memory performance and Hc volume in children across gestational age, birth weight, and SES.** As discussed above, the Hc is essential for episodic memory (Scoville & Milner, 1957); however, the relationship between Hc volume and memory performance is not well understood, especially in young children. The purpose of this aim is to investigate the potential relationships between Hc volume and episodic memory performance based on the results of Aim 2. The volume-performance relationships will be investigated for total Hc, Hc subregions (head, body, and tail) and Hc subfields (EC, CA1-2, CA3-DG, and subiculum).

**Hypothesis 3a.** It is hypothesized that neither the total Hc nor Hc subregion volumes will display a significant relationship with memory performance in young children, but the subfields will be differentially related to performance such that CA3-DG will be related to associative memory.

It is known that both premature birth and low SES can negatively impact cognitive and brain development, but little is known about the effect of premature birth and SES on the brain-behavior relationships. The volume-performance relationships will also be investigated across degree of prematurity and SES.

**Hypothesis 3b.** It is hypothesized that degree of prematurity will affect the relationships, but it is difficult to make any specific hypotheses, as so little is known about these effects.

**Hypothesis 3c.** Similarly, it is hypothesized that SES will affect the relationships, but it is difficult to make any specific hypotheses, as so little is known about these effects.

## CHAPTER 2 METHODS

### Participants

Sixty-eight young children (ages 5-7 years) from the metro-Detroit, Michigan area were recruited to participate in this study. Each child was recruited as part of one of two subsamples. The first subsample (“Preterm”) consisted of only preterm born children and was recruited from a cohort of a previous study (i.e. Raz, S. et al., 2016), in which participants were recruited directly from the neonatal intensive care unit (NICU) at William Beaumont Hospital in Royal Oak, Michigan. The second subsample (“Community”) consisted of near-term and term born children recruited through the Wayne State University (WSU) Pipeline and flyers handed out in the community. Importantly, individuals from the Preterm subsample were recruited for the cognitive tasks even if they opted out of participating in the MRI component of the current study. Individuals in the community sample were recruited if they initially agreed to participate in both the cognitive tasks and the MRI component of the current study. All participants were allowed to opt out of any portion of the study following recruitment. Fifteen participants either opted out of, or were ineligible for, the MRI portion of the study (twelve Preterm; three Community). Three participants completed the MRI session but either had incomplete or inadequate MRI data (one Preterm; two Community). Additionally, two participants from the Community subsample were excluded from all analyses due to brain abnormalities. Therefore, the final sample size was 48 with MRI data (20 Preterm; 28 Community) and 66 with cognitive data (33 Preterm; 33 Community).

While the overall sample size was smaller than would be recommended by a power analysis for some of the intended analyses, a larger balanced, sample size was not feasible as all preterm born participants were recruited from a previous cohort. It is important to note, however, that this sample size is consistent with similar published works (e.g., Briscoe & Gathercole, 2001).

Moreover, by using degree of prematurity as a continuous variable, the concerns of a small sample size were further decreased.

### **Demographics**

**Degree of prematurity.** Gestational age, birth weight, and birth weight relative to gestational age (“relative birth weight”; Oken, 2003) were all investigated separately. Gestational age was defined as the number of weeks and days from the first day of the mother’s last menstrual cycle until birth. Birth weight was the weight of the infant at birth, reported in grams. The percentile of relative birth weight was estimated using the participants information compared to a sample of over 6.5 million singletons born in the United States in 1999 and 2000 (Oken, 2003). This percentile measure was used to investigate the possibility that being born small for gestational age (SGA; percentile < 5) resulted in more neurocognitive deficits than being born average for gestational age (Padilla et al., 2011). As medical charts were only available for the Preterm subsample, gestational age and birth weight were extracted from the medical charts for the Preterm subsample and reported by the parents for the Community subsample. These variables were entered as continuous variables to capture potential differences across the Preterm subsample, as neurocognitive outcomes have been shown to increase in severity as the degree of prematurity increases (Briscoe & Gathercole, 2001; Brunnemann et al., 2013).

**Socioeconomic status.** SES was collected by parent report for both subsamples. Parents reported on household income, mother and father education, mother and father occupation, and computer experience/exposure. The education and occupations variables were coded using the four-factor model (Hollingshead, 2011). Parents also responded to a subjective SES measure of where their family’s status would be compared to other families in the United States on a 10-point scale (MAS; <http://www.macses.ucsf.edu/>).

## Testing Sessions Overview

The participants completed two 3- to 4-hour sessions, which were made child-friendly with techniques such as a space theme, positive reinforcement of stickers, and numerous practice sessions (Barnea-Goraly et al., 2014; Raschle et al., 2009). The cognitive assessment session was completed on the Wayne State University campus and included an initial exposure to an artificial MRI scanner if necessary (i.e., anxious child, active child, etc.). This initial exposure allowed the child to practice remaining motionless in the MRI.

The MRI session was completed at Harper Hospital in Detroit, Michigan and consisted of MRI training, the MRI scan, and additional cognitive assessments. During the MRI training, the child's ability to remain motionless was monitored with a temporal motion-tracking device. This practice was completed in an artificial MRI scanner that mimicked the sounds of the MRI and included a response box and video screen similar to those in the real MRI scanner. The participants were compensated for their time at a rate of \$30 for the MRI scan and \$15 per hour for all other time. In addition to compensation, the parents were provided a report of the standardized cognitive assessment results and screenshot images of their child's brain.

## Brain Measures

**MRI acquisition and post-acquisition processing.** The following T1 and T2 sequences, which were adopted from a previous study (Bender et al., 2013), were collected using a 32-channel head coil in a 3 Tesla Siemens Verio (Siemens Medical AG, Erlangen, Germany) scanner at Harper-Hutzel Hospital, Wayne State University (WSU). Both sequences were acquired in the coronal plane, perpendicular to the anterior-posterior commissural axis. Analyze v11.0 (Biomedical Imaging Resource, Mayo Clinic College of Medicine, Rochester, MN, USA) was used to complete all preprocessing and manual demarcation of all images.



Hc volume and intracranial volume (ICV) measures were taken from a T1-weighted magnetization prepared rapid gradient echo (MPRAGE) sequence. The T1 MPRAGE sequence was acquired with the following parameters: echo time = 4.26 ms; repetition time = 2200 ms; inversion time = 1200 ms; flip angle = 9.0°; pixel bandwidth = 130 Hz/pixel; GRAPPA acceleration factor PE = 2; interpolated voxel size 0.5 mm × 0.5 mm × 1.0 mm. The T1 image set was corrected for inhomogeneity and resampled to a 0.5 mm<sup>3</sup> isotropic voxel. Then the images were realigned manually to be perpendicular to the horizontal axis, so that the interhemispheric fissure was aligned. Manual correction was also applied to individual differences in tilt and roll.

The Hc subregion and subfield measures were taken for a T2-weighted turbo spin echo (TSE) proton density (PD) sequence. The T2 TSE PD sequence was acquired with the following parameters: echo time = 17 ms; repetition time = 7150 ms; flip angle = 120°; pixel bandwidth = 96 Hz/pixel; turbo factor 11; interpolated voxel size 0.4 mm × 0.4 mm × 2.0 mm; limited field of view 280 x 512 mm. The intensities of the T2 TSE PD image set were inverted so that the images were visually similar to those of the T1 image set.

**Hippocampal volumetry.** All images were displayed (magnified × 2) on a 21-inch digitizing tablet (Wacom Cintiq) and a stylus was used for manual demarcation. All independent raters were required to meet high reliability standards with an intra-class correlation coefficient (ICC(2)) (Shrout & Fleiss, 1979) of at least 0.85 for all hemispheric measures and 0.90 for all bilateral totals. All raters were blind to subsample status for manual demarcation.

Manual demarcation for the total Hc volume was modified from procedures developed by Raz and colleagues (Raz, N., Rodrigue, Head, Kennedy & Acker, 2004). The Hc volume was measured in the coronal plane on every third slice and extend from the mammillary bodies to the

most posterior slice on which the pulvinar nucleus was still visualized. Hc volume was the sum of the area across all 15 – 22 measured slices and the computed volume from the omitted slices.

Manual demarcation for the Hc subregions was complete according to Daugherty et al. (2015). The Hc head, body, and tail were measured in the coronal plane on every slice extending from the mammillary bodies to the point when the fornix and splenium of the corpus callosum was visualized and the left and right columns of the fornix were not fused based on the protocol by Daugherty et al. (2015). The Hc head range terminated when the Hc digitations were no longer visual and consisted of 2 – 4 slices. The Hc body range terminated when the fimbria fornix was visualized and consisted of 9 – 13 slices. The Hc tail terminated when the fornix and splenium were visualized and will consisted of 2 – 4 slices.

Manual demarcation for the Hc subfields and entorhinal cortex was adapted and modified from previous research (Mueller et al., 2007; Mueller & Weiner, 2009; Shing et al., 2011). The regions of interest included entorhinal cortex, CA1-2, CA3-DG, and subiculum. The subfields were measured in the coronal plane on every slice extending from the point that the uncus apex was no longer visualized to the most posterior slice where the lamina quadrigemina were visualized. The subfields were demarcated on 6 – 8 slices and span the length of the Hc body. The entorhinal cortex consisted of six slices, starting five slices anterior to the start of the Hc subfields. The CA1-2 – subiculum boundary was a vertical line perpendicular to the parahippocampal gyrus and the CA1-2 – CA3-DG and dentate gyrus boundary extended laterally to the subiculum. The medial boundary of the subiculum was a horizontal line that extended from the most medial parahippocampal white matter to the cerebrospinal fluid space. The CA3-DG was an ovoid-shaped region included all remaining Hc tissue.

**Intracranial volume measurement and volumetry correction.** Intracranial volume (ICV) was measured from the T1 MPRAGE image set. All images were displayed on the same tablet as for Hc demarcation (Wacom Cintiq) and the same stylus was used for manual demarcation. All independent raters were required to meet the same high reliability standards for manual demarcation of ICV as was required for the Hc measures. ICV was measured in axial plane as described in Raz et al. (2004). ICV was demarcated on every 20<sup>th</sup> slice, beginning with the most dorsal slice on which brain tissue was visualized and extending for 10 slices. All Hc measures were corrected for individual differences in ICV via analysis of variance (Jack et al., 1989), such that  $\text{volume}_{\text{adj}} = \text{volume}_i - b (\text{ICV}_i - \text{ICV}_{\text{mean}})$ , where  $i$  represented the individual's volume measurement,  $b$  represented the unstandardized coefficient of the sample regressed on ICV, and  $\text{ICV}_{\text{mean}}$  represented the mean ICV for the entire sample. General linear modeling (GLM) analysis was used to test for ICV by age, sex, and subsample interactions separately. The ICV correction was completed for the entire sample unless significant interactions were observed.

### **Standardized Cognitive Assessment**

**WPPSI-IV.** Seven subtests from the Wechsler Preschool and Primary Scale of Intelligence, fourth edition (WPPSI-IV), a standardized measure intended for children ages 2 – 7 years, was administered to participants. These seven subtests were chosen so that the Working Memory Index (WMI) and the Full-Scale Intelligence Quotient (FSIQ) could be calculated.

The WMI was comprised of two subtests: Picture Memory and Zoo Locations. The WMI was intended to measure the participants ability to store and recognize or reproduce visual information within a short time frame (Wechsler, 2012); however, both subtests required memory for associations (item-item and item-location) and were therefore are hypothesized to measure episodic memory. The Picture Memory subtest consisted of alternating stimulus pages and test

items. The participants viewed each stimulus page for three or five seconds, depending on difficulty, and completed the corresponding test item immediately. The images that were not unique to each item, as the same images repeated on multiple times. The stimulus pages consisted of 1 – 7 different target images. The test items consisted of the target stimuli and additional foil stimuli. The participants completed items until they responded incorrectly to three consecutive test items.

The Zoo Locations subtest consisted of a learning period (viewed the item for 3 – 5 seconds) and a testing period (replicated the item from memory). Each item consisted of animal cards placed in specific locations on a grid. The first trial included one animal in a 2x1 grid and the items increased in difficulty up to seven animals in a 3x3 grid. The same animals were repeated multiple times throughout the subtest but never more than once in a single item. When the animals were used again they did not always stay in the same location on the grid. Participants continued to complete items until they completed two consecutive test items incorrectly. Performance on both subtests was evaluated based on participants' accuracy.

The FSIQ was comprised of six subtests: Picture Memory, Information, Similarities, Bug Search, Block Design, and Matrix Reasoning. The FSIQ was intended to be an overall measure of the participants cognitive functioning (Wechsler, 2012). The Picture Memory subtest was described above. The Information subtest consisted of general knowledge questions that the participants were required to answer either by pointing to the correct picture or by verbally stating the answer. The Similarities subtest required the participant to explain how two words or pictures were similar. The Bug Search subtest was a timed task that required the participant to identify and mark pictures of bugs that matched the target picture. Bug Search was intended to be a measure of processing speed (Wechsler, 2012). The Block Design subtest was also a timed task that required

that participants to construct a design identical to the provided design. The Block Design subtest was intended to measure the participants ability to analyze and recreate visual information (Wechsler, 2012). The Matrix Reasoning subtest required the participants to identify the missing object or design that completed the provide pattern. The Matrix Reasoning subtest was intended to measure fluid reasoning (Wechsler, 2012).

The WMI and both subtests had strong internal consistency (WMI  $r_{xx} = .91$ ; Picture Memory  $r_{xx} = .91$ ; Zoo Locations  $r_{xx} = .86$ ) and moderate validity ( $r = .26-54$ ) with other standardized measures (Differential Ability Scales, second edition and A Developmental Neuropsychological Assessment, second edition; Wechsler, 2012).

**CVLT-C.** The California Verbal Learning Test, children's edition (CVLT-C), a standardized measure intended for children ages 5 – 16 years, was utilized to measure verbal memory. The CVLT-C included a list of 15 words from 3 semantic categories (Delis, Kramer, Kaplan, & Ober, 1994). There were 5 learning trials with a verbal presentation of the list followed by verbal free-recall by the participant. The presentation order was constant across trials. During the free recall phase, the participants were instructed to “say them in any order- just say as many of them as you can” (Delis et al., 1994, p. 11). The task did include a distraction trial, a short-delay trial, a long-delay trial, and a recognition trial; however, this study only used the data from the total free recall from the initial five trials.

This task had acceptable psychometric properties including strong average across-trial recall consistency ( $\alpha = .85$ ) and strong average across-word recall consistency ( $\alpha = .81$ ). In addition, this task had acceptable validity as evidenced by an exploratory factor analysis that resulted in a General Verbal Learning factor made up of factor loadings from all of the recall trials,

and a significant correlation ( $r = .33$ ) with a verbal subtest (Vocabulary subtest of Wechsler Intelligence Scale for Children-Revised; Delis et al., 1994).

**Picture sequence.** The NIH Toolbox Picture Sequence Memory Task (Picture Sequence) is summarized here, for a full description of the task see Bauer et al. (2013). Picture Sequence was administered on a computer, through the Internet. This task included a practice phase and two test items. All images were in color and represented actions (i.e. “bake the cake”) and all images of one trial corresponded to a common theme (i.e. “how to have a birthday party”). The images were presented one at a time in the center of the screen. An audio recording stated the action of each picture and the pictures were presented in a fixed order. Each image was assigned a unique location on the outer edge of the computer screen. The practice phase consisted of two different themes of four images each. The test phase consisted of two trials of the same theme of nine pictures. Performance on Picture Sequence task was evaluated by the participants’ ability to place the images in the correct consecutive ascending order.

This task had moderate convergent validity with a sentence repetition task (A Developmental Neuropsychological Assessment, second edition;  $r(110) = .50, p < .001$ ) but poor discriminant validity with a vocabulary task (Peabody Picture Vocabulary Test, fourth edition;  $r(112) = .58, p < .001$ ) with younger participants (Bauer et al., 2013). Despite this validity concern with young participants, this task was utilized because Picture Sequence was a unique measurement of memory in that it required recall of the content and location of an image.

**CAS.** Four subtests from the Cognitive Assessment System (CAS), a standardized measure intended for children ages 5 – 17 years, were administered. These four subtests were chosen so that the Attention Scale and the Planning Scale could be calculated. The Planning Scale was also comprised of two subtests: Matching Numbers and Planned Codes. The Planning Scale was

intended to measure implementation of a strategy and efficiency of problem solving (Naglieri & Das, 1997). The Matching Number subtest consisted of two timed items. The participants were required to visually scan several rows of numbers and identify the two identical numbers. The numbers increased from one digit to three digits. The Planned Codes subtest consisted of two timed trials. The participants were required to write a two-part code for four different letters based on a specified code (i.e. A has XX, B has XO, etc.) and the specified code was different for each trial.

The Attention Scale was comprised of two subtests: Number Detection and Expressive Attention. The Attention Scale was intended to measure selective attention for target stimuli and inhibition of competing stimuli (Naglieri & Das, 1997). The Number Detection subtest consisted of two timed items. The participants were required to visually scan several rows of numbers and identify every instance of the three target numbers (i.e. mark every 1, 2, or 3). The three target numbers were different in each trial. Performance on both subtests was evaluated based on accuracy (number correct) and efficiency (speed of response). The Expressive Attention subtest consisted of three timed items. All items required the participant to verbally state whether each animal was big or small based on the animal that was pictured (i.e. elephants are big; frogs are small). In the first non-interference item, all of the pictures were the same size; in the second non-interference item, the pictures were proportional to the animal (i.e. a big picture of an elephant and a small picture of a frog); in the interference trial, the animals were either the correct proportion or opposite proportions (i.e. a small picture of an elephant) and the participant always had to state the size of the animal despite the size of the picture.

The Planning Scale and the Attention Scale both had acceptable reliability. For example, the Attention Scale reliability for age 5 was  $\alpha = .84$  and for age 6 it was  $\alpha = .74$ . In addition, the individual subtests had sufficient reliability: Expressive Attention (age 5  $\alpha = .80$ ; age 6  $\alpha = .64$ )

and Number Detection (age 5  $\alpha = .76$ ; age 6  $\alpha = .72$ ). While the two subtest scores were moderately correlated ( $r = .35$ ), they may not measure the same construct. In a confirmatory factor analysis, the factor loadings for Expressive Attention and Number Detection were .37 and .81. Additionally, the two subtests did not load onto the same factor in an exploratory factor analysis (Naglieri & Das, 1997). These validity concerns indicated that the data should be analyzed at the subtest level to check construct validity before using the Attention Scale as a combined measure of executive function.

**Card sort.** The NIH Dimensional Change Card Sort administered on a computer, through the Internet. Card sort intended to measure cognitive flexibility and attention. This task consisted of a practice phase and three test phases: color, shape, and mixed. During all phases the participant provided with two response pictures and asked to sort a target picture to one of the response options be either color or shape. The participant first asked to sort based on color only than the participant asked to sort based on shape only. If the participant successful at these tasks (8 out of 10 trials correct), they administered the mixed test phase. The mixed test phase consisted of 30 items that mostly color sorts with shape sorts intermittently presented. Performance on this task was evaluated based on time required to sort the items and accuracy of the sort.

### **Experimental Cognitive Assessment**

In addition to a wide range of standardized assessments, this study also utilized a range of more specialized tasks that were designed to test more specific aspects of cognition.

**Picture-pair.** Associative Line Drawing Memory (Picture-Pair), a computerized experimental task developed in the Ofen lab, was designed to test associative memory and was adapted specifically for assessment in young children (Daugherty & Ofen, 2015). Picture-Pair consisted of a practice trial and two test trials. Each test trial consisted of a study phase, a 1-minute



distraction task of counting, and a test phase. The stimuli used for this task were 132 black line drawings within a  $2\frac{5}{8} \times 2\frac{5}{8}$  inch white square.

The study phase of test trial consisted of 26 drawing pairs each presented for 5 seconds with a 1-second inter-item interval. The test phase had both an item recognition task and a pair recognition task. The stimuli were presented with a black background on a 13-inch MacBook Pro laptop with a resolution of 1280 x 800 and a refresh rate of 60 Hz. During the study phase and the pair recognition task, the drawings were presented 3-inches apart on opposite sides of the screen. During the item recognition task, the single drawing appeared in the center of the screen. The presentation order of the study phase and the task order of the test phase were both counterbalanced based on participant number. The first and last drawing pairs from the study phase were removed from the testing phase, as they may have been encoded differently due to their position in the presentation order.

The item recognition task consisted of 16 individual line drawings. Half of these drawings were shown in the study phase (target drawings) and half were new (foil drawings). The participant was required to state if they saw the image before or not. The pair recognition task consisted of 16 drawing pairs and included only drawings that were presented during the study phase. Half of the pairs in the pair recognition task were presented as they were in the study phase (complete pairs) and half were comprised of two drawings that were not paired together in the study phase (recombined pair). The participant was required to state if the pair was a complete pair or a recombined pair. Performance on both recognition tasks was evaluated based on correct recognition of target images/pairs (hits) and recognition errors (false alarms). As this was an experimental task, no validity or reliability measures were available.

**Object memory.** Object Memory, a computerized experimental task developed in the Ofen lab and adapted for children, was designed to measure recognition for objects. Object memory consisted of a practice item and two test items. Each test item consisted of a study phase, a 1-minute distraction task of counting, and a test phase. The stimuli were 256 color-images of objects. Half the stimuli were equally distributed into eight distinct object categories (i.e. bread, cars, etc.) while the other half of the stimuli were from unique object categories. There were an additional six images used only during the study phase for an image repetition task (an n-back task) to keep the participants engaged during the study phase. For this n-back task, the two duplicate images were only be separated by zero, one, or two target images but the participant was not aware of these options.

The study phase consisted of 70 randomly presented images (64 target images and 3 images for the n-back task). Each image was presented for three seconds and there was a 1-second inter-trial interval between each image. Half of the target images were from 4 distinct object categories (within category images) and half were from unique categories (across category images). The images were presented with a black background on a 13-inch screen with a resolution of 1280 x 800 and a refresh rate of 60 Hz. The image set was counterbalanced based on participant number.

The test phase consisted of a two alternative-force choice task (2AFC) and an old-new recognition task. The order of these tasks was counterbalanced based on participant number. The 2AFC task consisted of 32 trials of one target image and one foil presented simultaneously. Half of the 2AFC trials were within-category trials where the foil and the target image were from the same object category and half of the trials were across category trials where the foil was from a different category than the target image. The participant was required to select the target image for both within-category and across category trials. The old-new recognition task consisted of 64

images presented individually. Half of the old-new trials were target images and half were foils. The participant was required to indicate if the image was “old” (target image) or “new” (foil). Half of the images during the old-new task were with-category images and half were across-category images. Performance for both tasks was evaluated based on accuracy of detecting the target images for both within category trials and across category trials. As this was an experimental task, no validity or reliability measures were available.

### **Analytic Approach**

All data were screened for missing data, outliers, non-linearity, homoscedasticity, normality, and multicollinearity across the entire sample. Grouped data screening was not completed because all prematurity and SES variables were used as continuous variables in most analyses. Analyses were completed with and without the outliers any results that changed after removing the outliers are described in the results section. A few participants in the Community sample were missing birth weight ( $n = 5$ ) and/or gestational age ( $n = 8$ ) data. To improve power, this data was estimated based on a large sample of children born in the United States in 1999 and 2000 (Oken, 2003). Missing gestational age was imputed as 39.5 weeks as this was the average of a large sample (Oken, 2003). If a participant was also missing birth weight, the value of 3421g was imputed as this represents the 50<sup>th</sup> percentile for 39 weeks gestational age (Oken, 2003).

Independent sample t-tests were used to assess for potential group differences in demographic information, cognitive tasks, and Hc volumes between the two subsamples. Age and sex were included as covariates in all analyses and any variables that showed significant differences between subsamples were considered as potential additional covariates in analyses. Independent sample t-tests were also used to assess for potential differences in demographic and cognitive variables between those who had MRI data and those who did not have MRI data. A

repeated measure general linear modeling (GLM) analysis was completed to explore potential differences between the corrected volumes of the left and right hemispheres of all Hc measures and a total volume of both left and right was used for each Hc measure that did not display a significant hemisphere effect.

**Aim 1 – Analysis of volume of hippocampus, hippocampus subregions, and hippocampus subfields in young children across gestational age, birth weight, and SES.** A series of repeated measure GLMs were used to assess for potential differences in Hc volume across gestational age, birth weight, and SES. These analyses were initially set up with Hc volume as the dependent variable and gestational age, birth weight, relative birth weight, income, or computer experience as the sole covariate. Additional GLMs were completed with one prematurity variable, one SES variable, sex, and age as covariates in the same analysis. Although a region x hemisphere design would be more appropriate for this data, each region was analyzed separately due to concerns about small sample size and low power.

**Aim 2 – Assessment of construct validity of episodic memory tasks in young children across gestational age, birth weight, and SES.** A series of exploratory factor analyses were completed using Principal Component Analysis (PCA). The first PCA included only those variables expected to measure episodic memory and focused on evaluating the construct validity of episodic memory. The second PCA included measures of episodic memory and executive functioning. The third PCA included the only measures that loaded onto a memory factor of the first PCA. The additional PCAs focused on evaluating the discriminate validity of episodic memory tasks. The small sample size was considered when interpreting the factor loadings and, therefore, only strong factor loadings (0.55 and higher) were retained (Tabachnick, 2014). Additionally, as it is recommended that the analysis include at least five participants for every

variable, none of the factor analyses included more than fourteen variables ( $68/5 = 13.6$ ; MacCallum, 1999; Tabachnick, 2014).

As episodic memory and executive function are both aspects of overall cognition, it was anticipated that the factors would be correlated. Thus, an oblique rotation with  $\Delta = 0$  was used in all PCAs. A factor was defined as any component with an Eigenvalue greater than 1.00 (i.e. Crawford et al., 2010) and the number of factors retained by the Eigenvalue method was confirmed using the Scree Plot. The PCAs included the whole sample so that the relationships between the resulting factor scores and measures of prematurity could be evaluated in aim three. Once a memory-related factor was established, independent sample t-tests were used to assess for potential group differences in factor scores. Additionally, a series of GLMs were used to for potential differences in factor scores across gestational age, birth weight, and SES.

**Aim 3 – Assessment of relationship between memory performance and hippocampal volume in young children across gestational age, birth weight, and SES.** Univariate GLMs were conducted to evaluate the relationship between Hc volumes and the factor scores found in aim two across gestational age, birth weight, and SES similar to the analyses for Aim 1. The GLMs were initially set up with the factor scores from Aim 2 as the dependent variables and Hc volume as the dependent variable. For all significant relationships, an additional GLM was completed with gestational age, birth weight, or relative birth weight, as well as SES, sex, and age as additional covariates. Just as in Aim 1, each Hc region was analyzed separately.

## CHAPTER 3 RESULTS

## Subsample Characteristics

As expected the Preterm subsample had significantly lower gestational age ( $t = -18.30, p < .01$ ) and birth weight ( $t = -18.61, p < .01$ ) compared to the Community subsample (see Table 1). Interestingly, the two subsamples did not differ on relative birth weight ( $t = -1.43, p = .16$ ). It is important to note that, unexpectedly, relative birth weight displayed a significant positive correlation with age in the overall sample ( $p = .02$ ). Therefore, any results involving relative birth weight or age should be interpreted with caution. Although the two subsamples did not differ on the over measure of SES ( $t = 0.30, p = .76$ ), the Preterm subsample had significantly higher income ( $t = 2.32, p = .02$ ) and parent-rated computer experience scores ( $t = 2.35, p = .02$ ) than the Community subsample.

Table 1  
*Comparison Between Preterm and Community Subsamples on Demographic Variables*

Variable	Preterm		Community		t (p)
	Mean (SD)	Min-Max	Mean (SD)	Min-Max	
Sex (Male:Female)	14:19		18:17		$\chi^2=0.55 (.46)$
Singleton:Twin	16:17		--		--
Gestational Age (GA)	30.18 (2.52)	24.7-33.7	39.22 (1.30)	36.5-42.5	<b>-18.30 (&lt;.01)</b>
Birth weight (BW)	1326.33 (375.54)	580-1935	3237.94 (455.23)	2296-4054	<b>-18.61 (&lt;.01)</b>
Relative BW Small for GA	33.97 (22.29) n = 4	2-83	42.33 (25.22) n = 3	1-90	-1.43 (.16)
Age	6.15 (0.56)	5.14-7.04	6.04 (0.66)	5.05-7.04	0.71 (.48)
Overall SES	51.89 (10.29)	32.0-66.0	51.01 (12.89)	22.0-66.0	0.30 (.76)
Mother Education	5.88 (1.11)	4-7	6.12 (1.083)	3-7	-0.90 (.37)
Father Education	5.79 (1.08)	4-7	5.31 (1.31)	3-7	1.60 (.12)
Mother Occupation	6.12 (2.63)	0-9	4.72 (3.67)	0-9	1.77 (.08)
Father Occupation	6.67 (2.33)	2-9	6.75 (2.36)	0-9	-0.14 (.89)
Subjective SES	6.38 (1.16)	4-9	6.25 (1.90)	1-9	0.32 (.75)
Yearly Income	8.44 (1.16)	5-9	7.58 (1.73)	2-9	<b>2.32 (.02)</b>
Computer Exp.	17.17 (2.71)	10-21	15.30 (3.43)	10-21	<b>2.35 (.02)</b>

Left Hc volume ( $t = 3.34, p < .01$ ) and left head volume ( $t = 4.21, p < .01$ ) were significantly larger in the Preterm subsample compared to the Community subsample (See Table 2).

Table 2  
*Comparison Between Preterm and Community Subsamples on Brain Volumes*

Variable	Preterm		Community		t (p)
	Mean (SD)	Min-Max	Mean (SD)	Min-Max	
ICV	1544754.00 (101406.70)	1345930- 1726590	1547341.43 (104939.84)	1374950- 1781240	-0.09 (.93)
Hc Left	3348.83 (348.76)	2899.52- 3994.74	3057.53 (256.71)	2653.81- 3654.77	<b>3.34 (&lt;.01)</b>
Hc Right	3280.36 (398.54)	2670.41- 4118.11	3133.82 (238.99)	2676.31- 3611.27	1.59 (.12)
Head Left	1320.58 (171.46)	1058.91- 1650.74	1060.94 (234.60)	724.48- 1610.08	<b>4.21 (&lt;.01)</b>
Head Right	1318.80 (265.84)	910.95- 1903.11	1211.85 (250.57)	751.84- 1680.55	1.42 (.16)
Body Left	1188.42 (157.16)	848.35- 1504.11	1176.20 (103.33)	1005.93- 1391.37	0.33 (.75)
Body Right	1139.66 (174.09)	836.15- 1424.21	1108.60 (117.65)	915.98- 1367.47	0.74 (.46)
Tail Left	301.49 (70.77)	191.19- 474.69	311.79 (105.16)	145.51- 590.15	-0.38 (.71)
Tail Right	313.79 (105.44)	160.77- 548.65	313.65 (83.56)	148.19- 463.87	0.01 (>.99)
EC Total	590.64 (89.41)	405.33- 767.44	617.04 (82.06)	449.06- 871.08	-1.06 (.30)
DG Left	295.13 (36.51)	228.28- 348.64	297.34 (51.60)	229.73- 479.63	-0.16 (.87)
DG Right	282.85 (36.97)	218.27- 357.46	284.25 (46.94)	222.42- 449.30	-0.11 (.91)
CA1-2 Left	254.21 (33.09)	206.06- 311.22	258.99 (38.40)	188.48- 373.88	-0.45 (.66)
CA1-2 Right	277.77 (29.59)	231.76- 347.85	281.66 (41.37)	213.89- 400.91	-0.36 (.72)
Subiculum Total	841.28 (108.53)	693.53- 1097.80	805.66 (92.42)	651.21- 1006.70	1.22 (.23)

The Preterm subsample had a significantly lower Working Memory Index Standard Score ( $t = -2.23, p = .03$ ; see Table 3) as a result of lower Zoo Locations performance. There were no other significant differences between the two subsamples.

Table 3  
*Comparison Between Preterm and Community Subsamples on Cognitive Performance*

Variable	Preterm		Community		t (p)
	Mean (SD)	Min-Max	Mean (SD)	Min-Max	
Block Design Raw	23.15 (2.99)	16-30	23.58 (4.74)	17-34	-0.435 (.67)
Information Raw	22.91 (1.93)	19-29	22.94 (2.79)	16-28	-0.52 (.96)
Matrix Reason Raw	16.73 (4.79)	4-24	17.33 (4.2)	7-25	-0.55 (.59)
Bug Search Raw	35.33 (9.30)	16-52	33.58 (9.62)	10-57	0.76 (.45)
Picture Mem. Raw	15.91 (3.93)	9-24	16.88 (4.80)	8-26	-0.90 (.37)
Similarities Raw	28.00 (5.48)	11-36	28.70 (6.58)	5-38	-0.47 (.64)
Zoo Locations Raw	10.76 (1.98)	7-15	11.64 (3.61)	7-14	-1.93 (.06)
VCI	108.64 (12.00)	85-141	112.82 (17.39)	73-143	-1.14 (.26)
WMI	97.27 (11.73)	88-141	103.85 (12.27)	76-129	<b>-2.23 (.03)</b>
FSIQ	105.79 (10.09)	83-124	110.18 (17.08)	73-143	-1.27 (.21)
Trial 1-5 Correct	34.06 (9.61)	11-49	33.85 (10.08)	5-47	0.09 (.93)
Picture Sequence	433.11 (96.04)	305.73- 598.99	425.33 (80.21)	305.73- 598.99	0.32 (.75)
Pair Cancel. Raw	25.21 (9.23)	9-43	22.25 (9.06)	7-53	1.31 (.20)
Match Number Raw	7.44 (2.81)	3-13	7.15 (2.76)	2-15	0.41 (.68)
Planned Codes Raw	14.35 (8.64)	2-38	16.03 (9.79)	2-40	-0.72 (.47)
Express Atten. Raw	37.63 (12.06)	15-63	35.12 (9.72)	15-51	0.91 (.36)
Number Detect Raw	22.07 (8.77)	5-41	19.64 (10.44)	4-45	1.00 (.32)
Item d'	2.24 (0.91)	0.00-4.31	1.91 (0.96)	-0.16-4.31	1.43 (.16)
Pair d'	0.72 (0.81)	-0.52-2.42	0.41 (0.57)	-0.52-1.64	1.76 (.08)
O/N W d'	1.01 (0.78)	-0.65-2.38	1.07 (0.79)	-1.80-2.52	-0.30 (.77)
O/N A d'	2.16 (1.04)	0.63-3.71	2.04 (1.24)	-1.87-4.04	0.38 (.71)
2AFC W Acc	0.79 (0.12)	0.44-0.97	0.81 (0.12)	0.41-0.97	-0.51 (.61)
2AFC A Acc	0.89 (0.12)	0.50-1.00	0.86 (0.15)	0.44-1.00	0.76 (.50)

*Note.* O/N=Old-New; W=Within category; A=Across Category; 2AFC=Two Alternative Force Choice; Acc = Accuracy or the proportion of correct out of total trials.

The Preterm subsample were still recruited if they opted out of the MRI, but the Community subsample was only recruited if they initially agreed to complete both the MRI and the cognitive portions. Therefore, it is not a surprise that the group with MRI data had significantly higher gestational age ( $t = 2.99, p < .01$ ) and birth weight ( $t = 2.86, p < .01$ ) than those without MRI data (See Table 4). There was no difference, however, between those with MRI data and those without MRI data on relative birth weight ( $t = 0.81, p = .42$ ). There was also a significant sex difference between those with MRI and those without ( $X^2 = 6.09, p = .01$ ) such that the proportion of females in greater in the MRI group than in the MRI group. The group with MRI



data had significantly higher overall SES ( $t = 2.13, p = .04$ ), which was partially due to a significantly greater father occupation score ( $t = 2.54, p = .02$ ) than the no MRI group.

Table 4

*Comparison Between Participants with and without MRI Data on Demographic Variables*

Variable	With MRI		Without MRI		t (p)
	Mean (SD)	Min-Max	Mean (SD)	Min-Max	
Sex (Male:Female)	27:21		4:14		$\chi^2=6.09$ <b>(.01)</b>
Preterm:Community	20:28		13:5		$\chi^2=4.89$ <b>(.03)</b>
Gestational Age (GA)	35.76 (4.51)	27.1-42.5	31.88 (5.16)	24.7-40.1	<b>2.99 (&lt;.01)</b>
Birth weight (BW)	2496.65 (986.89)	940-4054	1710.11 (1016.47)	580-3856	<b>2.86 (&lt;.01)</b>
Relative BW	39.63 (24.11)	1-90	34.22 (23.90)	4-83	0.81 (.42)
Age	6.11 (0.61)	5.05-7.04	6.05 (0.63)	5.14-6.90	0.36 (.72)
Overall SES	53.30 (10.99)	22-66	46.67 (11.96)	26-66	<b>2.13 (.04)</b>
Mother Education	6.08 (1.01)	4-7	5.78 (1.31)	3-7	1.01 (.32)
Father Education	5.77 (1.20)	3-7	5.00 (1.09)	4-7	<b>2.36 (.02)</b>
Mother Occupation	5.32 (3.39)	0-9	5.72 (2.87)	0-9	-0.45 (.66)
Father Occupation	7.21 (1.91)	0-9	5.39 (2.81)	2-9	<b>2.54 (.02)</b>
Subjective SES	6.35 (1.73)	1-9	6.22 (1.06)	4-8	0.29 (.78)
Yearly Income	8.06 (1.58)	2-9	7.87 (1.36)	5-9	0.43 (.67)
Computer Exp.	15.74 (3.18)		17.68 (3.04)		<b>-2.02 (.05)</b>

Importantly, the participants that have MRI data did not differ on any cognitive measure compared to those without MRI data (see Table 5). However, when only the Preterm subsample was considered, those with an MRI had significantly higher birth weight ( $p = .02$ ), overall SES ( $p < .01$ ), Father education ( $p < .01$ ), father occupation ( $p < .01$ ), income ( $p < .01$ ), and block design raw score ( $p = .03$ ). However, there was no difference in gestational age ( $p = .08$ ).

### ICV Correction and Hemispheric Differences

Significant ICV by sex interactions were observed for Hc body (left  $p < .01$ ; right  $p = .04$ ; total  $p = .01$ ), DG (left  $p = .02$ ; right  $p = .01$ ; total  $p = .02$ ), and CA1-2 (left  $p = .05$ ; right  $p = .03$ ; total  $p = .03$ ). No ICV by age and ICV by subsample interactions were significant. Therefore, total

Hc, head, tail EC, and Subiculum were corrected across the entire sample but body, DG, and CA1-2 were corrected separately by sex.

Table 5  
*Comparison Between Participants with and without MRI Data on Cognitive Performance*

Variable	With MRI		Without MRI		t (p)
	Mean (SD)	Min-Max	Mean (SD)	Min-Max	
Block Design Raw	23.63 (4.16)	17-34	22.67 (3.31)	16-28	0.88 (.38)
Information Raw	22.77 (2.43)	16-29	23.33 (2.14)	19-28	-0.87 (.39)
Matrix Reason Raw	17.17 (4.66)	4-25	16.67 (4.06)	7-22	0.40 (.67)
Bug Search Raw	34.81 (9.65)	10-57	33.50 (9.01)	16-51	.50 (.62)
Picture Mem. Raw	16.56 (4.78)	8-26	15.94 (3.15)	11-23	.61 (.55)
Similarities	27.88 (6.46)	5-38	29.61 (4.58)	20-36	-1.04 (.30)
Zoo Locations Raw	11.29 (1.99)	7-15	10.94 (1.63)	8-13	0.66 (.51)
VCI	109.73 (15.79)	73-143	113.39 (12.55)	85-137	-0.88 (.38)
WMI	101.15 (12.57)	76-129	99.00 (11.99)	79-121	0.64 (.53)
FSIQ	108.08 (14.95)	73-143	107.72 (11.89)	87-133	0.09 (.93)
Trial 1-5 Correct	33.65 (10.29)	5-49	34.78 (8.45)	17-48	-0.42 (.68)
Picture Sequence	425.46 (88.10)	305.73- 598.99	438.65 (90.51)	305.73- 598.99	-0.49 (.63)
Pair Cancel. Raw	23.45 (9.34)	7-53	24.56 (9.03)	9-43	-0.43 (.67)
Match Number Raw	7.42 (2.79)	2-15	6.94 (2.75)	3-13	0.61 (.55)
Planned Codes Raw	15.79 (9.72)	2-40	13.65 (7.67)	4-33	0.82 (.41)
Express Atten. Raw	36.96 (11.16)	15-63	34.59 (10.21)	15-49	0.76 (.45)
Number Detect Raw	21.00 (10.16)	4-45	20.24 (8.50)	5-41	0.28 (.78)
Item d'	2.01 (0.94)		2.25 (0.95)		-0.92 (.36)
Pair d'	0.47 (0.66)		0.82 (0.80)		-1.81 (.08)
O/N W d'	0.74 (0.17)		0.78 (0.12)		-0.69 (.49)
O/N A d'	1.98 (1.13)		2.65 (1.08)		-1.53 (.13)
2AFC W Acc.	0.80 (0.13)		0.80 (0.06)		-0.11 (.91)
2AFC A Acc.	0.87 (0.15)		0.88 (0.05)		-0.17 (.87)

The GLMs assessing for potential differences between the left and right hemisphere resulted in a significant hemisphere by subsample interaction for total Hc ( $p = .03$ ) and Hc head ( $p = .02$ ). There was a significant hemisphere by sex interaction for DG ( $p < .01$ ) and CA1-2 ( $p < .01$ ). There was a significant hemisphere by age interaction for Hc body ( $p = .050$ ) and Hc tail ( $p = .04$ ). Therefore, separate left and right measurements were used for Hc, head, body, tail, DG, and CA1-2 but a total of the two hemispheres was used for EC and Subiculum.

## Aim 1 – Volume of the Hc in Young Children Across Gestational Age, Birth Weight, and SES

**Volume of Hc Total.** A series of repeated measure GLMs were run with left and right Hc volumes. Hc volumes did not differ across gestational age, birth weight, relative birth weight, income, or computer experience ( $p = .10 - .62$ ). However, there was a significant hemisphere interaction with gestational age ( $F(1, 46) = 4.02, p = .05$ ; Figure 14) and birth weight ( $F(1, 46) = 4.78, p = .03$ ; Figure 15) such that the right hemisphere Hc volume displayed a slightly stronger positive relationship with the preterm variables than the left. The hemisphere interaction was still significant when correcting for birth weight and other covariates (age, sex, and income:  $F(1, 42) = 5.78, p = .02$ ; age, sex, computer experience:  $F(1, 42) = 4.80, p = .03$ ) but were no longer significant when correcting for gestational age and other covariates ( $p = .06 - .07$ ). There were no other significant effects on Hc volume.

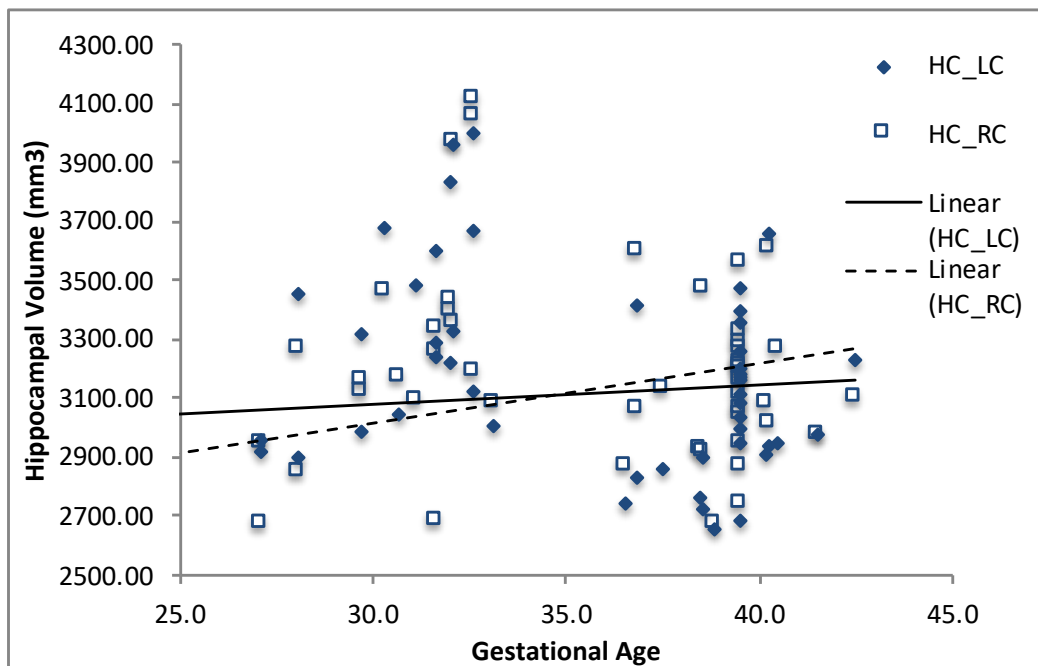


Figure 14. The relationship between corrected total Hc volume and gestational age.

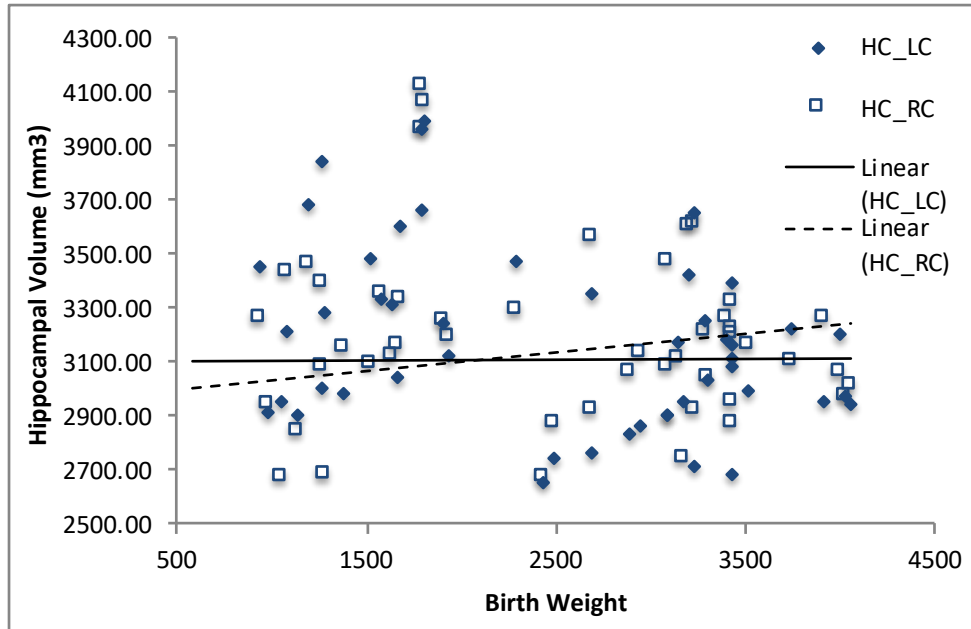


Figure 15. The relationship between corrected total Hc volume and birth weight.

**Volume of Hc Subregions: Head, Body, Tail.** A series of repeated measure GLMs were completed with left and right Hc head, body, and tail volumes separately. Hc head volume was significantly larger for individuals with lower gestational age ( $F(1, 46) = 5.82, p = .02$ ; Figure 16) and smaller birth weight ( $F(1, 46) = 9.23, p < 0.01$ ; Figure 17).

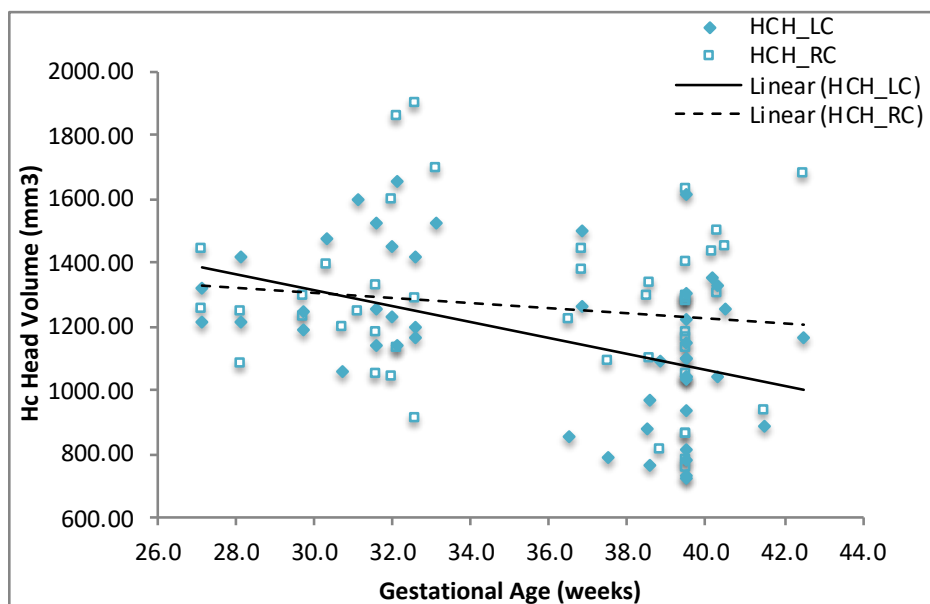


Figure 16. The relationship between corrected Hc head volume and gestational age.

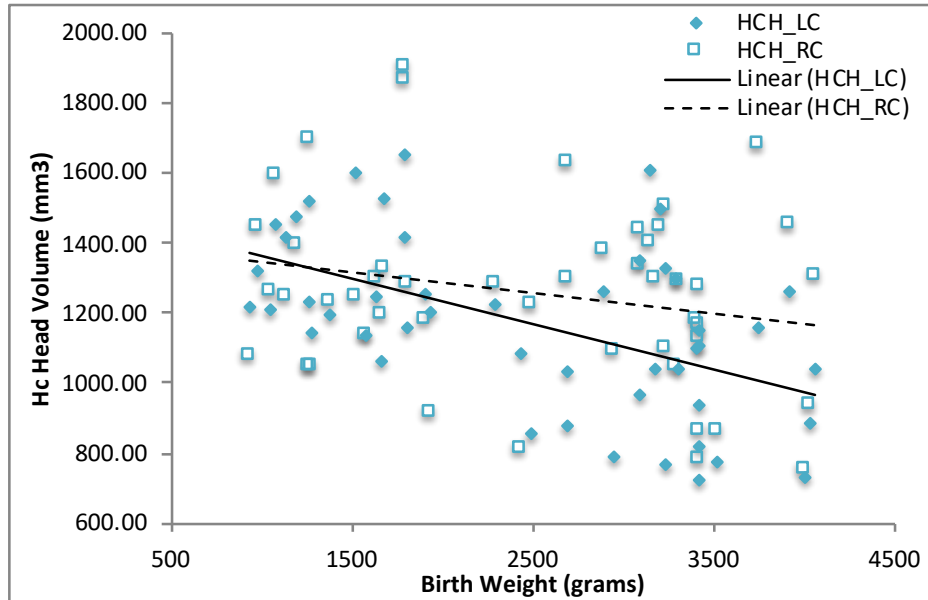


Figure 17. The relationship between corrected Hc head volume and birth weight.

Head volume did not differ across relative birth weight ( $p = .07$ ), income ( $p = .23$ ), or computer experience ( $p = .13$ ). There were significant hemisphere interactions with gestational age ( $F(1, 46) = 5.90, p = .02$ ) and birth weight ( $F(1, 46) = 4.58, p = .04$ ). After correcting for the prematurity variables, SES variables, age, and sex; the birth weight main effects were still significant (income:  $F(1, 42) = 4.37, p = .04$ ; computer experience:  $F(1, 42) = 9.06, p < .01$ ). The hemisphere by birth weight interaction effect was only significant when income was used as the SES variable (income:  $F(1, 42) = 5.04, p = .03$ ; computer experience:  $F(1, 42) = 3.52, p = .07$ ). Alternatively, the main effect for gestational age was only significant when computer experience was used as the SES variable (income:  $F(1, 42) = 3.65, p = .06$ ; computer experience:  $F(1, 42) = 6.55, p = .01$ ) but the hemisphere by gestational age interaction effects were significant in both models (income:  $F(1, 42) = 5.30, p = .02$ ; computer experience:  $F(1, 42) = 4.32, p = .04$ ).

Contrary to Hc head volumes, Hc body volumes did not differ across degrees of prematurity ( $p = .36 - .67$ ) or SES ( $p = .35 - .44$ ). There were significant hemisphere by age

interactions ( $F = 3.98 - 5.11, p = .05 - .03$ ; Figure 18) such that right body volume showed a slight positive relationship with age but left did not. Additionally, there was a significant hemisphere interaction with computer experience ( $F(1, 45) = 4.41, p = .04$ ; Figure 19) such that the right body volume displayed a slight negative relationship with computer experience. This effect was still significant after correcting for prematurity, age, and sex ( $F = 4.63 - 5.89, p = .04 - .02$ ).

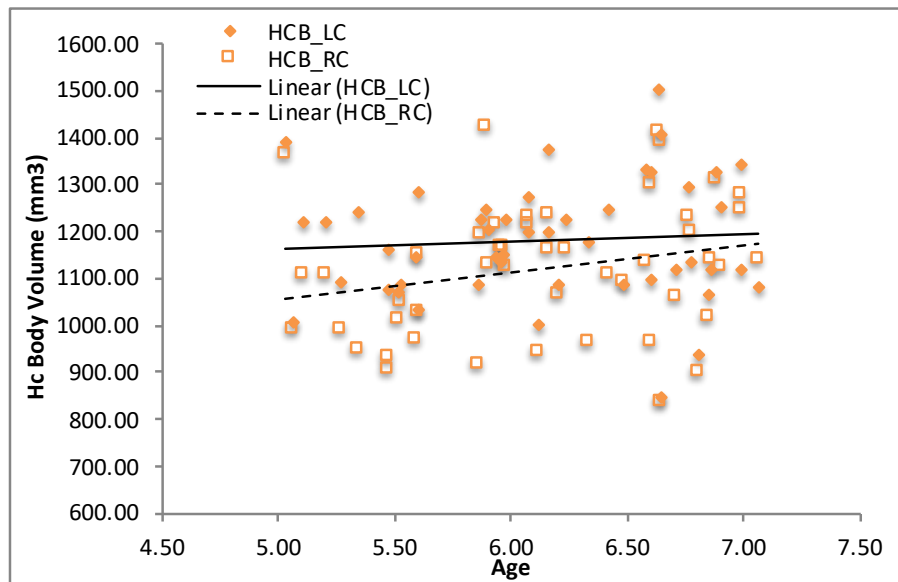


Figure 18. The relationship between corrected Hc tail volume and relative birth weight.

Hc tail volumes did not differ across degrees of prematurity ( $p = .30 - .66$ ) or SES ( $p = .30 - .66$ ). There was a significant interaction between hemisphere and relative birth weight ( $F(1, 46) = 4.41, p = .04$ ; Figure 20) such that the left tail volume displayed a slight positive relationship with relative birth weight, but right volume did not. Importantly, this effect is likely due the significant correlation between relative birth weight and age. The interaction with relative birth weight was no longer significant after correcting for additional covariates but the hemisphere interactions with age were significant ( $F = 4.07 - 5.01, p = .05 - .03$ ; Figure 21).

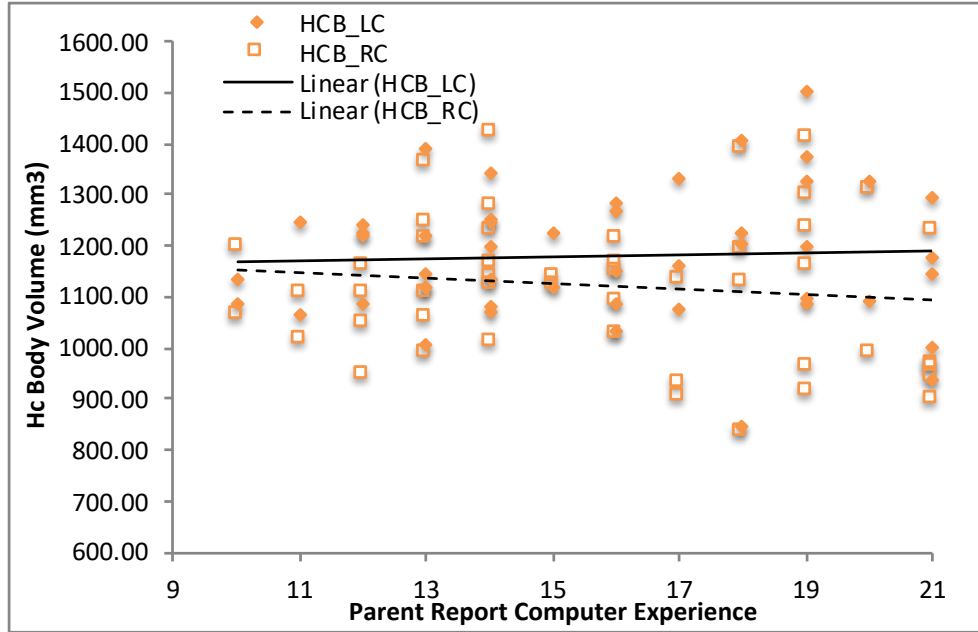


Figure 19. The relationship between corrected Hc body volume and computer experience.

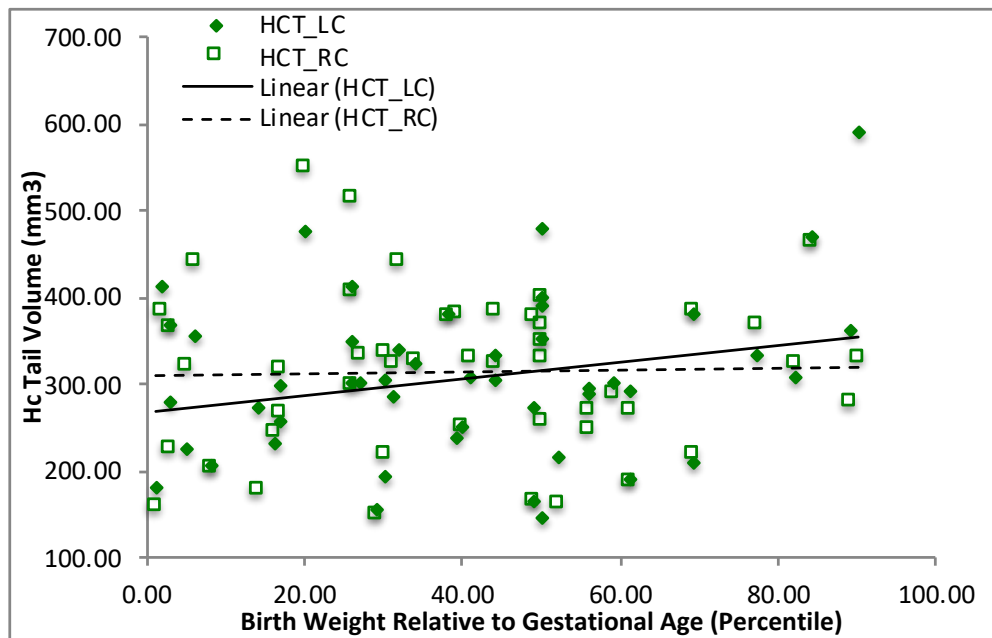


Figure 20. The relationship between corrected Hc tail volume and relative birth weight.

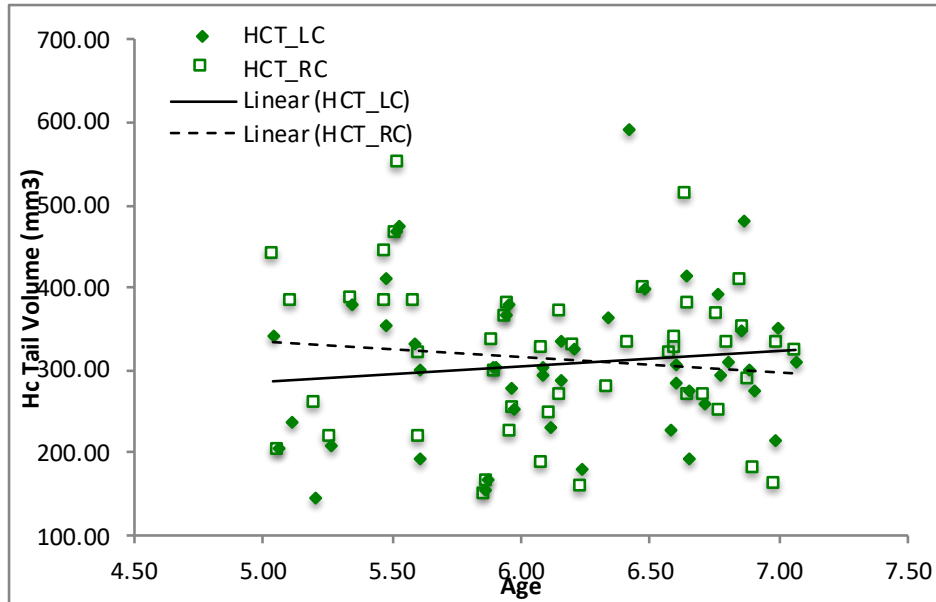


Figure 21. The relationship between corrected Hc tail volume and age.

**Volume of Hc Subfields: Subiculum, CA1-2, CA3-DG.** A series of univariate GLMs were run with total EC and subiculum volumes and additional repeated measure GLMs were run with left and right CA1-2 and CA3-DG volumes. There was no difference in any of the subfield volumes across gestational age ( $p = .18 - .80$ ), birth weight ( $p = .26 - .75$ ), relative birth weight ( $p = .69 - .80$ ), income ( $p = .26 - .97$ ), or computer experience ( $p = .34 - .92$ ). However, when correcting for prematurity, SES, age, and sex, there were significant hemisphere by sex effects for CA1-2 ( $F = 7.95 - 11.63$ ,  $p < .01$ ; Figure 22) and CA3-DG ( $F = 19.03 - 21.98$ ,  $p < .01$ ; Figure 23). These significant sex effects are difficult to interpret due to the small sample size. Future studies are needed with larger samples before any interpretation is possible.

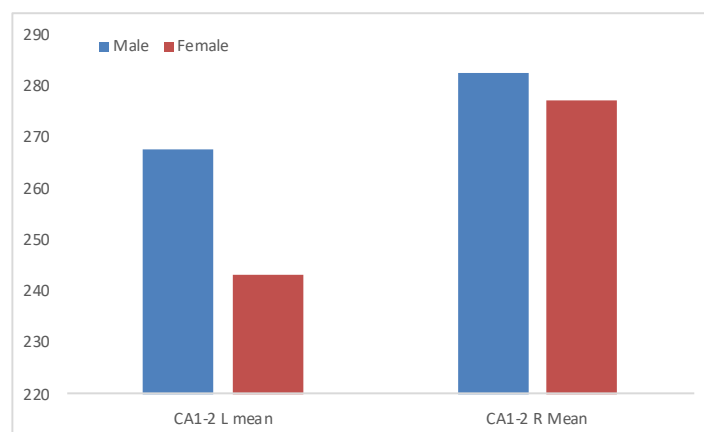
### Aim 2 – Construct Validity of Episodic Memory Tasks in Young Children

A series of exploratory PCAs were completed to investigate the construct validity of episodic memory. The first PCA included several tasks hypothesized to measure episodic memory performance (See Appendix C). This analysis resulted in three factors with strong loadings (See Figure 24). The first factor, which included tasks that required recall or recognition of single items



or paired items (CVLT total recall, picture-pair item recognition, picture-pair pair recognition, and object memory old/new recognition), was termed the Memory factor. The second factor, which included tasks that required processing speed and working memory (Zoo Locations, Picture Memory, and Picture Sequencing), was termed the Lower-Level Executive Function (Low EF) factor. The third factor, which included tasks that required making more complex decisions (object memory 2AFC), was termed the Higher-Level Executive Function (High EF) factor. Although the factor loadings are strong, and this factor structure is theoretically clear, these factor scores should be interpreted with some caution because the three-factor structure resulted 53% of the residuals in the reproduced correlations table being greater than 0.05.

A second PCA was completed with additional executive function tasks added to the tasks from the first PCA. This second PCA resulted in a five-factor structure (See Table 6) but the tasks did not separate based on a clear theoretically model, which was likely due to having too many variables for the sample size. A third PCA was completed with only the tasks that loaded onto the Memory factor in the first PCA to confirm the cohesiveness of the factor. This analysis did result in only one factor and all tasks had strong factor loadings as expected (results not shown because same as Memory factor in first PCA).



*Figure 22.* Corrected CA1-2 volume by sex.

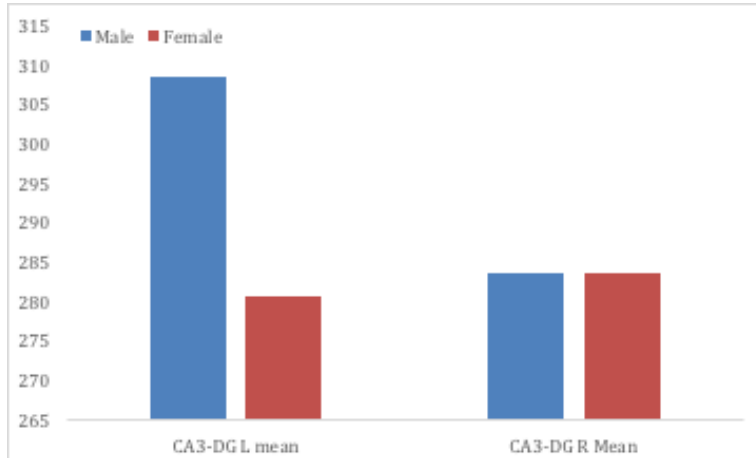


Figure 23. Corrected CA3-DG volume by sex.

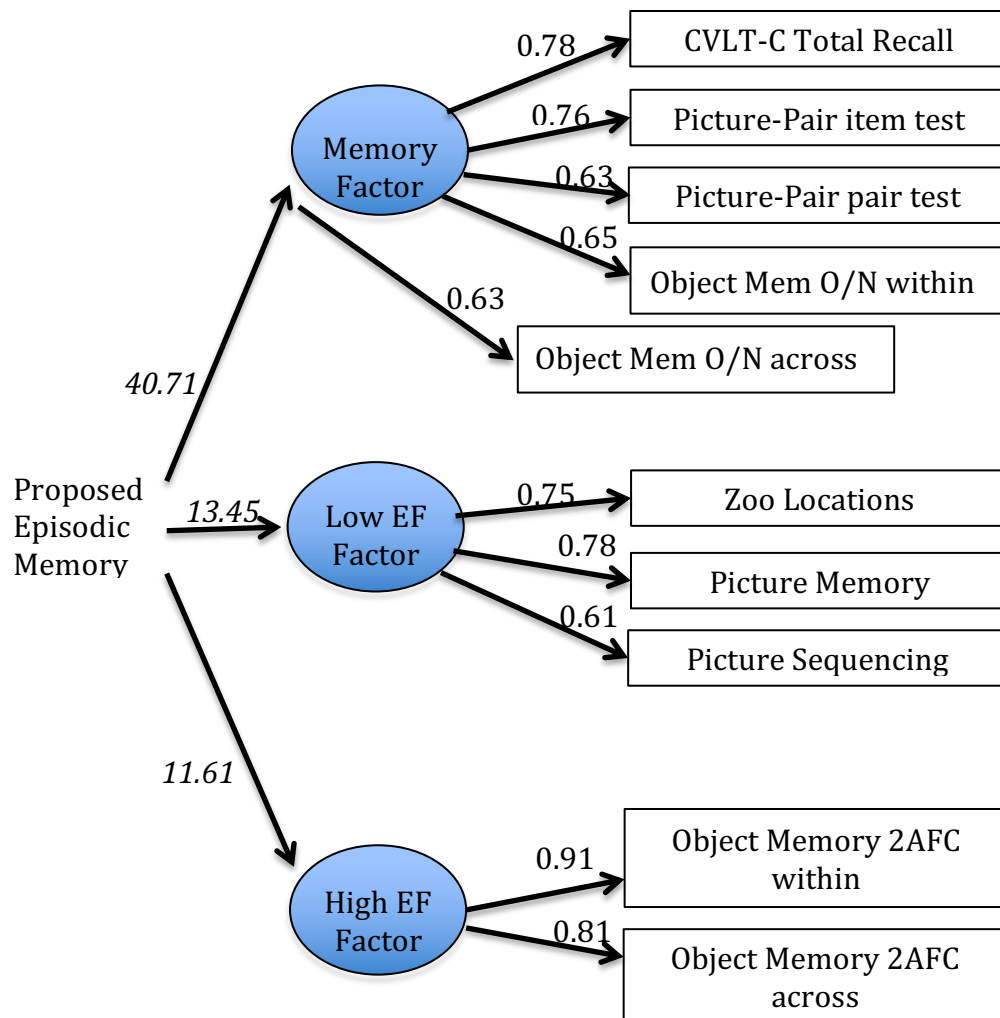


Figure 24. Observed outcome for first episodic memory factor analysis.

O/N = old/new. The numbers in italics indicate the percent of variance account for in each factor.

The non-italicized numbers indicate the factor loading of each individual task onto each factor.

Table 6  
*Factor Structure for PCA 2 with Memory and Executive Function tasks*

Task	Factor 1	Factor 2	Factor 3	Factor 4	Factor 5
Zoo Locations Raw				.61	
Picture Memory Raw	.80				
CVLT Total 1-5	.54	-4.9			
Picture Sequencing	.51				
Item d' Average					.734
Pair d' Average					.89
O/N Within d'		-.92			
O/N Across d'		-.84			
2AFC Within d'			-.78		
2AFC Across d'			-.88		
Expressive Attention	.79				
Number Detection	.74				
Card Sort				.90	

*Note.* O/N=Old-New; W=Within category; A=Across Category; 2AFC=Two Alternative Force Choice

The three factors from the first PCA were used for t-tests and GLMs to investigate for potential differences across degree of prematurity and SES. There were no significant group differences between the Preterm subsample and the Community subsample on any of the factor scores (See Table 7). The Low EF factor increased as relative birth weight increased ( $F(1, 40) = 5.62, p = .02$ ; See Figure 25). No other factor scores differed across gestational age ( $p = .43 - .99$ ),

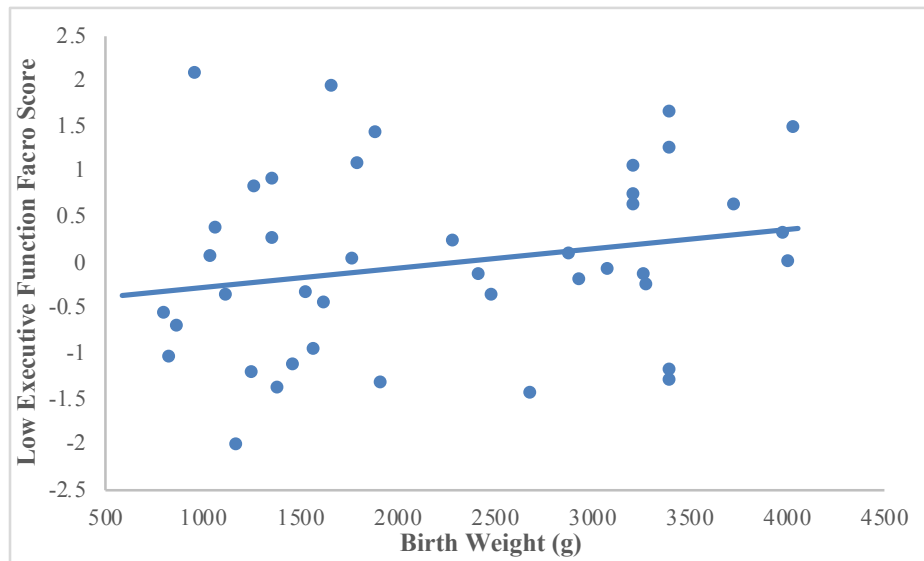
birth weight ( $p = .17 - .92$ ), relative birth weight ( $p = .40 - .48$ ), income ( $p = .33 - .53$ ), or computer experience ( $p = .34 - p = .15$ ).

Table 7

*Comparison Between Preterm and Community Subsamples on Factor Scores*

Variable	Preterm		Community		t (p)
	Mean (SD)	Min-Max	Mean (SD)	Min-Max	
Memory Factor, PCA1	0.07 (1.08)	-2.24-1.76	-0.08 (0.92)	-2.38-1.22	0.50 (.62)
Low EF Factor, PCA1	-0.12 (1.12)	-2.01-2.07	0.14 (0.86)	-1.45-1.63	-0.85 (.40)
High EF Factor, PCA1	-0.03 (1.01)	-1.34-3.12	0.04 (1.02)	-1.12-3.31	-0.21 (.83)
Memory Factor, PCA3	0.08 (1.12)	-2.31-1.86	-0.08 (0.89)	-2.18-1.27	0.55 (.59)

*Note.* EF = Executive Function. The Memory factor from PCA1 and from PCA3 contain the same tasks, difference is that PCA1 included additional tasks that loaded on the EF factors and PCA3 only contained the Memory factor.



*Figure 25.* The relationship between birth weight and the Low EF factor scores.

### **Aim 3 – Volume of the Hc and Memory Performance in Young Children**

Univariate GLMs were completed for the whole sample as a first step to investigate the potential relationship between the Hc volumes (as determined above, Aim 1) and memory performance (as determined above in the factor scores, Aim 2). Of all Hc subregions and subfields, Hc body (Left:  $F(1, 32) = 4.27, p = .05$ ; Right:  $F(1, 32) = 5.46, p = .03$ ; See Figure 26), CA3-DG (Right:  $F(1, 32) = 4.49, p = .04$ ; See Figure 27), and subiculum (Total:  $F(1, 32) = 5.05, p = .03$ ;

See Figure 28) were significantly related to the Memory factor as smaller volumes were related to better performance. Neither of the EF factors were significantly related to any Hc volumes.

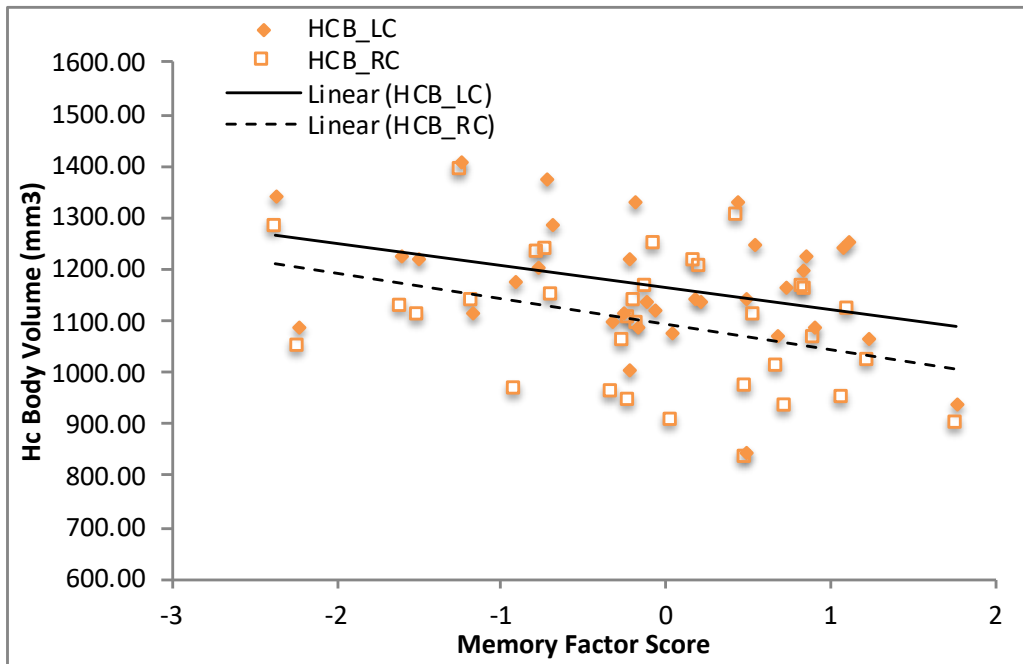


Figure 26. The relationship between corrected Hc body volume and Memory factor scores.

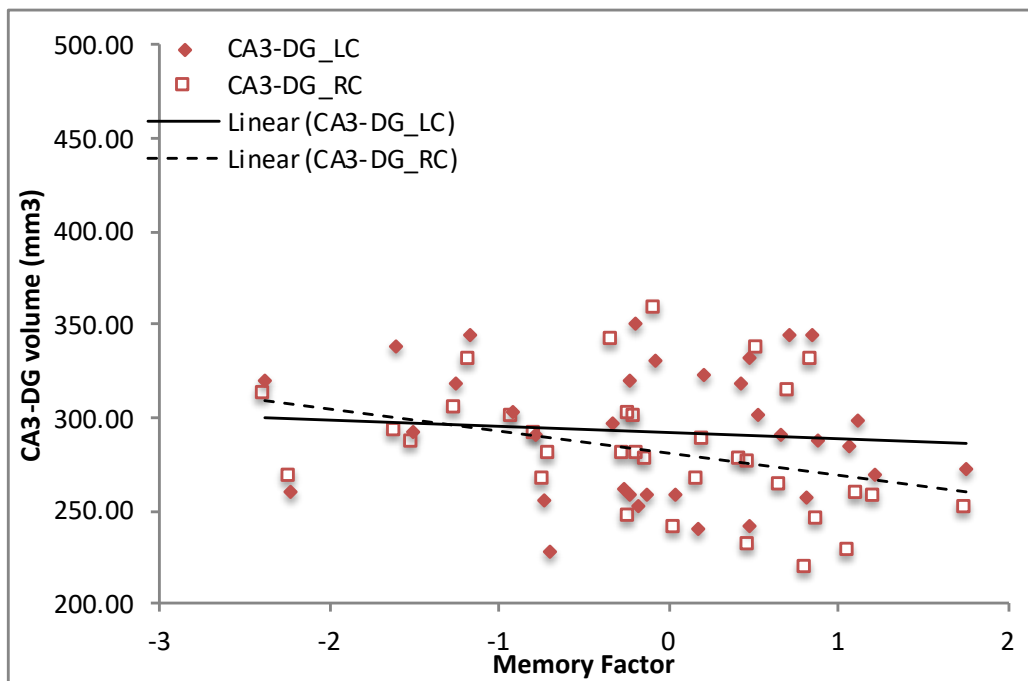


Figure 27. The relationship between corrected CA3-DG volume and Memory Factor scores.

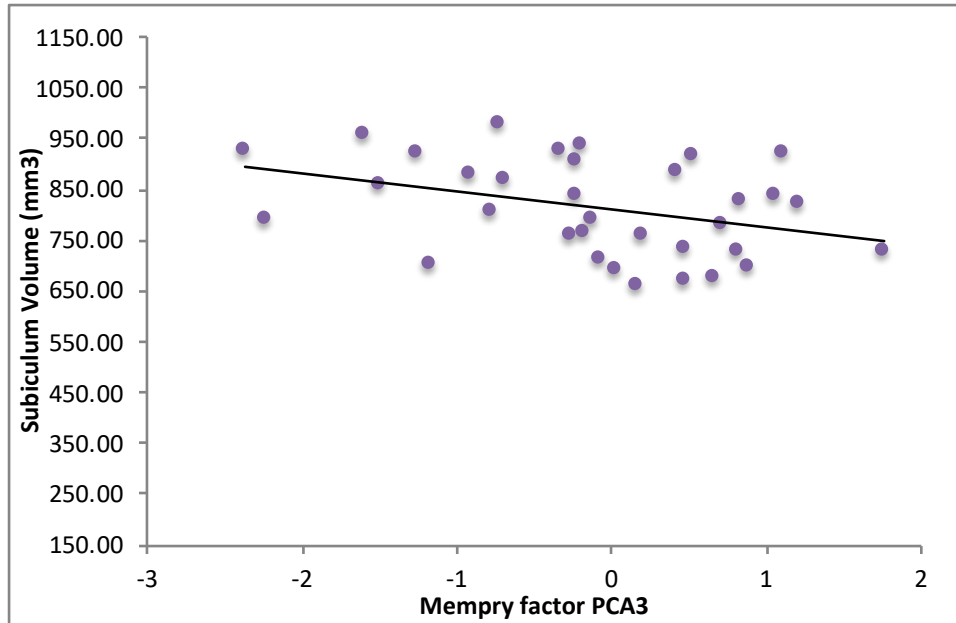


Figure 28. The relationship between corrected Subiculum volume and Memory Factor scores.

The volume-performance relationships also remained significant for most analyses after simultaneously correcting for degree of prematurity, SES, age, and sex for body (Left:  $F = 4.47 - 4.72$ ,  $p = .04$ ; Right:  $F = 5.48 - 6.14$ ,  $p = .03 - .02$ ); however, after correcting for computer experience, left body volume was no longer significantly related to the Memory factor ( $p = .08$ ). The relationship between DG right and the Memory factor also remained significant after correcting for degree of prematurity, SES, age, and sex ( $F = 4.00 - 10.02$ ,  $p < .01 - .06$ ) as did the relationship with subiculum ( $F = 5.47 - 7.06$ ,  $p = .03 - .01$ ). Overall, the main effects of degree of prematurity ( $p = .13 - .98$ ) and SES ( $p = .07 - .99$ ) were not significant in most models investigating the volume-performance relationships. Importantly, when investigating the relationship between CA3-DG and the Memory Factor, the main effect of income was significant when gestational age was included in the model  $F(1, 27) = 4.51$ ,  $p = .04$  and trending when birth weight was included  $F(1, 27) = 3.70$ ,  $p = .07$ .

## CHAPTER 4 DISCUSSION

In the current study, we assessed the effects of preterm birth on hippocampal volume and memory performance in 5-6-year old children. We found limited evidence for the effects of prematurity on brain structure and memory performance. In brief, I showed that the degree of prematurity was negatively related to the volume of the Hc head so that the lower the gestational age or birth weight, the larger the Hc head volume. Degree of prematurity was not significantly related to any other subregion or subfield volume. As for the aim of assessing episodic memory, I identified that a latent factor can be formed to represent episodic memory. Although no separate factors captured what can be considered an item compared to associate memory, with a factor analyses I identified factors that seem to capture differences in task characteristics that tax higher or lower demands for executive functions. Moreover, individual differences in a factor that requires low contribution of executive functions was related to the degree of prematurity. Alternatively, the degree of prematurity was not related to memory performance at this age. Finally, although we found relationships between Hc volume and memory performance, these relationships did not seem to differ by various measures of the degree of prematurity. SES was not related to Hc volume or memory performance; however, SES appears to have at least a minimal effect on the volume-performance relationship between CA3-DG and memory. Below I discuss these findings, highlighting the unique contribution they provide to the growing body of work investigating the effects of premature birth on development.

### **Premature Birth and Volume of the Hc**

There is growing interest in the effects of premature birth on brain development, specifically Hc development, but these effects are not fully understood. In the extant literature, there are reports of variable results when comparing corrected Hc volume between preterm born

and term born individuals. The pooled effect from the meta-analysis I completed indicated that preterm born have significantly smaller Hc volumes than term born individuals, even when corrected Hc volume is used. Nevertheless, there was minimal evidence from the meta-analysis and from published literature (Omizzolo et al., 2013) that suggested this decrease in Hc volume would not be present at the ages of 5-7 years. Therefore, it was not surprising that this sample did not show significant differences across degrees of prematurity. Additionally, none of the preterm born individuals that had an MRI had a history of extremely low birth weight (<750g), which would have made them more likely to display decreased Hc volume (Omizzolo et al., 2013; Taylor et al., 2011). Although degree of prematurity did not have an effect on Hc volume, the distribution of data shows that the Preterm subsample displayed more variability than the Community subsample. It is possible that this increased variability is related to individual differences in birth characteristics other than gestational age and birth weight, which may be more predictive of deficits.

It is possible that the significant effect in the head and the null effect in the CA1-2 subfield are driven by a higher proportion of the CA1-2 located in the head (Poppenk et al., 2013; Riggins et al., 2018) compared to the body where it was measured for this study. It was not possible to investigate the most anterior portions of the CA1-2. The subfields were only traced in the body because the manual tracing of the subfields is not as reliable in the head (Bender et al., 2013). It was anticipated that the more premature an individual was, the smaller their CA1-2 volume would be because CA1-2 is highly susceptible to hypoxic/ischemic events (Abernethy et al., 2002; Cooper et al., 2015; Schmidt-Kastner, 2015; Schmidt-Kastner, & Freund, 1991; Thompson et al., 2013) that are relatively common in preterm born infants. Additionally, these decreases in volume were also anticipated in the tail because previous research displayed deficits in posterior Hc (Cole



et al., 2015; Gimenez, 2004). However, that previous research was completed with adolescents and the protocols used less reliable measures (stereology and shape analysis). Therefore, it is not surprising that the results of this study are not commensurate to these previous studies, as the differences may relate to development or methodological differences. An interesting possibility to account for the increase in head volume, in preterm compared to term, is if increased volume is considered to represent a maladaptive pruning processes in this population (i.e. Taylor et al., 2011).

### **Premature Birth and Memory**

Previous research indicates that preterm born children display consistent deficits in several areas of cognition (Allotey et al., 2017). Therefore, it was hypothesized that degree of prematurity would be positively related to performance on the Memory factor. However, when the specific effects of premature birth on memory were investigate, as opposed to general effects on intelligence, preterm born individuals did not always display deficits, there is some evidence to suggest that only visual memory is impaired after premature birth (Omizzolo et al., 2013) or that only preterm born individuals with significant medical complications at birth will display memory deficits compared to healthy term born controls (Briscoe & Gathercole, 2001; Brunnemann et al., 2013). But most notably, the meta-analysis I completed prior to this study suggests that deficits in the volume-performance relationships may not be present until later in childhood following premature birth. Therefore, it is possible that the Memory factor would show deficits in adolescents who were born premature but not in this sample of young children.

The factor analysis also resulted in two factors that I identified as related to two theoretically clear executive function factors. These additional executive function factors highlight the importance of confirming construct validity prior to analyzing performance, as the tasks that loaded onto the executive function factors were originally thought to measure episodic memory.

Although the Memory factor was not associated with degree of prematurity, the Low EF factor was positively associated with relative birth weight.

### **Relationship Between Volume of the Hc and Memory Performance**

Current literature indicates that Hc head is positively related to memory at age 6 but not at age 4 (Riggins et al. 2015; Riggins et al., 2018) in term born participants, which emphasizes the importance of investigating this age range, as it is a time of rapid development. Current literature also indicates that CA3-DG is related to memory in term born children and adults (Daugherty et al., 2017; Lee et al., 2014), but little is known about these interactions in preterm born individuals. The negative volume-performance relationships were unexpected given the positive relationships that were observed in previous studies. However, this unexpected finding may be due to the young age of children in this sample. Importantly, the executive function factors were not related to Hc volumes, which is evidence for the specificity of Hc for memory functioning.

### **SES, Volume of the Hc, and Memory**

The null effect of SES on any measure of Hc volume when memory and SES were considered is consistent with previous research (Yu et al., 2017); however, the main effects of SES were anticipated to be significant. The lack of significant main effects of SES on Hc volume and memory performance may be due to the restricted range in this data set, particularly in the income variable. All but 8 from the Preterm subsample and 17 from the Community Subsample reported the highest possible income for this measure (>100,000 gross annual income). This null effect may also be due to the SES measures that were used. It is possible that a different measure of SES (i.e. access to health care) or a composite variable (i.e. Social Risk; Omizzolo et al., 2013) may have a significant impact on Hc volume. Additionally, it is apparent that different measures of SES interact with Hc and memory development differently because models that accounted for income

occasionally resulted in different patterns of results than those that accounted for computer experience. Importantly, although several measures of SES were used, it is possible that there is a difference in SES between subsamples that was not captured in this study, such as access to healthcare and therapeutic/corrective services.

### **Strengths and Limitations**

The meta-analysis that was completed in preparation for the current study included significantly more studies that measured Hc volume than a previous meta-analysis (deKieviet et al., 2012) and, more importantly, was the first meta-analysis to quantitatively assess the pooled effect of volume-performance relationships between Hc and cognition (intelligence and memory combined) in preterm born individuals. Similarly, the current study was influential, as it is one of the first studies to investigate the volume of hippocampal subregions and subfields in preterm born individuals during early childhood. Furthermore, the current study used highly reliable manual tracing to obtain all Hc volume measures, which is an improvement on the automatic tracing that is used in a large portion of current literature. Despite these strengths, these results should be considered preliminary due to several limitations, such as issues with researchers knowing term status, small sample size, suboptimal sample, and restricted range of SES.

The primary limitation to this study is that researchers are not blind to term-status during testing. Researchers knew subsample status because the Preterm subsample was recruited differently than the Community Subsample. Additionally, this knowledge was necessary for proper counterbalancing on the experimental tasks. The counterbalancing for these tasks was automated based on participant number (i.e. odd verses even) and providing the Preterm subsample and the Community subsample different types of numbers (300s and 100s) is the most efficient method

for proper counterbalancing. Importantly, the manual tracers responsible for collecting the Hc volumes were blind to term-status while tracing.

A second limitation is that, due to the nature of the sample, the sample size likely resulted in low power for some analyses. may not have sufficient power. However, the sample size was similar to that of previous literature and prematurity and SES variables were used as continuous variables to reduce concerns with sample size. Additionally, the Preterm subsample included several sets of twins, but all twins were used in all analyses due to concerns with sample size. Unfortunately, the techniques that increased sample size resulted in a somewhat suboptimal sample. Specifically, the two subsamples were distinct groups and there was a gap in data between the two subsamples on both gestational age and birth weight. Additionally, by including both individuals in twin-pairs there was decreased independence of data.

There were also a few characteristics of the participants that likely reduced generalizability of these findings. First, nearly all individuals in this study were in middle-to-upper class families that have sufficient or ample resources. Second, the Preterm subsample was subject to selection bias because the families that participated did so as an unanticipated follow-up to a study that was completed 2-3 years previously. This selection bias was intensified in the MRI sample because individuals with the highest degree of prematurity either opted out of the MRI or were unable to participate. Importantly, the Preterm subsample did not display deficits in certain areas of cognition that have consistently been decreased in preterm born individuals (i.e. intelligence).

### **Future Directions**

As this research is novel and the results are preliminary, it is important to continue to build off of this study into more advanced research. First it is important to investigate the volume-performance relationships between Hc volume and memory in preterm born individuals across all

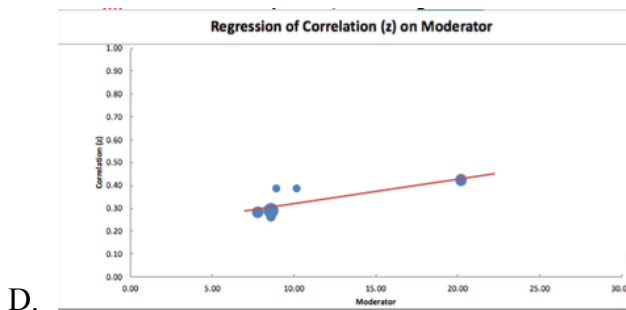
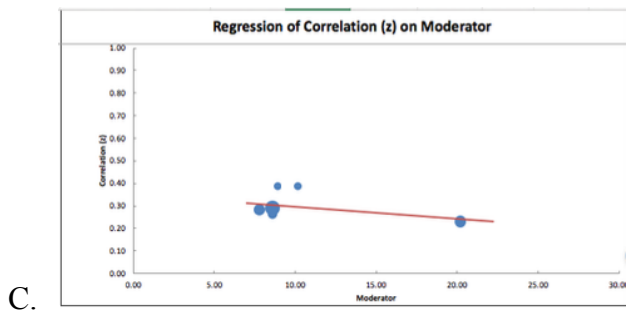
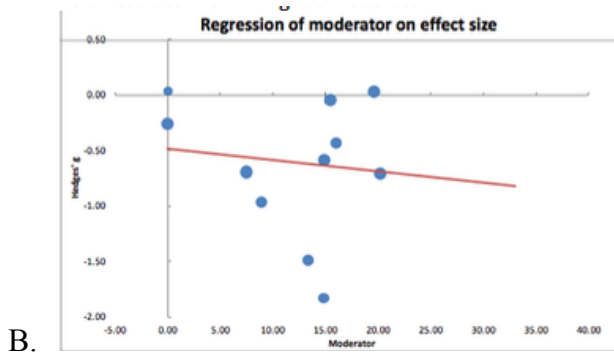
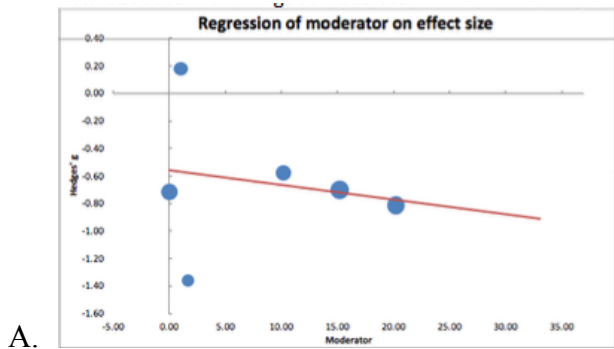
levels of SES. A larger sample size would allow for more in-depth analyses, such as investigating potential nonlinear effects, which is important as the distribution of data suggests there may be a nonlinear relationship between tail volume and degree of prematurity, especially for birth weight (See Appendix D). The factor analysis also resulted in two executive function factors and one area of future research is to determine if differences in these factors relate to differences in other brain regions (i.e. prefrontal cortex). Additionally, as there were several sets of twins in the Preterm subsample and twins display more neurocognitive deficits than singletons born prematurely (Raz, S., et al., 2016), it would be important to investigate if the twins also display more atypical Hc volumes and volume-performance relationships. Finally, it would be important to consider other birth characteristics beyond gestational age and birth weight to determine if there are certain risk factors or protective factors that predict more or less deficits later in life.

## Appendix A: Overview of Studies Included in the Meta-Analysis

Study	Term Participants	Preterm Participants	PT Age Mean	PT GA Mean	PT BW Mean	Measures Reported
Parikh et al. 2013	16	122	38.5w	26.7	771.0	Total U; Total C
Gousias et al. 2012	5	15	40w*	29.0*	NR	Left U; Right U;
Thompson et al. 2008	32	184	MRI=40.1w Cog=2	27.6	964.0	Left U; Right U; Total C; Left C; Right C
Padilla et al. 2011	15	15	12.6m	31.0	1580.0	Total U; Total C
Lowe et al. 2011	10	16	20.2m	28.1	1082.1	Total U; Total C
Lowe et al. 2012	10	12	43.1m	29.7	1152.2	Total C
Omizzolo et al. 2013	34	145	7.5	27.5	972.0	Left U; Right U;
Solsnes et al. 2016	103	36	7.8	29.0	1019.0	Total C; RelIQ
Peterson et al. 2000	39	25	8.6	28.7	997.4	Left C; Right C
de Kieviet et al. 2014	47	30	8.6	28.9	1186.0	Total C; RelIQ
Lodygensky et al. 2005	21	60	8.7	29.4	1280.0	Total C; RelIQ
Brunnemann et al. 2013	19	21	8.9	30.6	1360.0	Left U; Right U; Left C; Right C; RelVerb; RelVis
Arhan et al. 2017	24	22	9.1	29.6	1634.0	Total C
Brumbaugh et al., 2017	72	48	9.4	34-36^	2700.0	Total C
Gunewaldt et al. 2014	30	21	10.2	26.3	797.0	Total U; RelIQ
Fraello et al. 2011	20	49	12.3	28.4	972.7	Left C; Right C
Gimenez et al. 2004	22	22	13.3	29.4	NR	Left U; Right U; Left C; Right C
Isaacs et al. 2003	8	11	13.6	28.0*	998.0*	Left C; Right C
Gimenez et al. 2008	21	21	14.8	30.0	1375.4	Left U; Left C
Nosarti et al. 2002	48	66	14.9	29.6	1288.1	Left U; Right U; Left C; Right C
Martinussen et al. 2009	57	50	15.2	29.1	1205.0	Total U;
Cole et al. 2015	35	61	15.5	28.8	1248.3	Left U; Right U;
Abernethy et al. 2002	8	86	15-17^	28.6	1103.0	Left U; Right U;
Taylor et al. 2011	36	35	16.7	29.2	1147.1	Total C
Cheong et al. 2013	132	148	18	25.8	897.0	Total C
Cole et al. 2015'	35	61	19.6	28.8	1248.3	Left U; Right U; Total U; Left U; Right U;
Aanes et al. 2015	60	44	20.2	29.5	1234.0	Total C; Left C; Right C; RelVerb; RelVis
Fearon et al. 2004	18	33	23.2	<33*	1172.0	Left C; Right C
Meng et al., 2016	69	85	26.5	30.7	1355.8	Right C
Tseng et al. 2016	49	46	30	29.3	NR	Total C

Note. Age at Testing is reported in years unless otherwise stated; m = months; W = weeks gestation; \*= median; ^=range; NR=Not reported in study; U = Uncorrected volume; C = Corrected volume; RelVerb = Relationship between Hc volume and verbal memory ; RelVis = Relationship between Hc volume and visual memory; RelIQ = Relationship between Hc volume and intelligenc

## Appendix B: Age as Moderator in Meta-Analysis



Total Uncorrected (A); Left Uncorrected (B); IQ/Verbal Memory(C); IQ/Visual Memory (D)

## Appendix C: Episodic Memory Task Descriptions

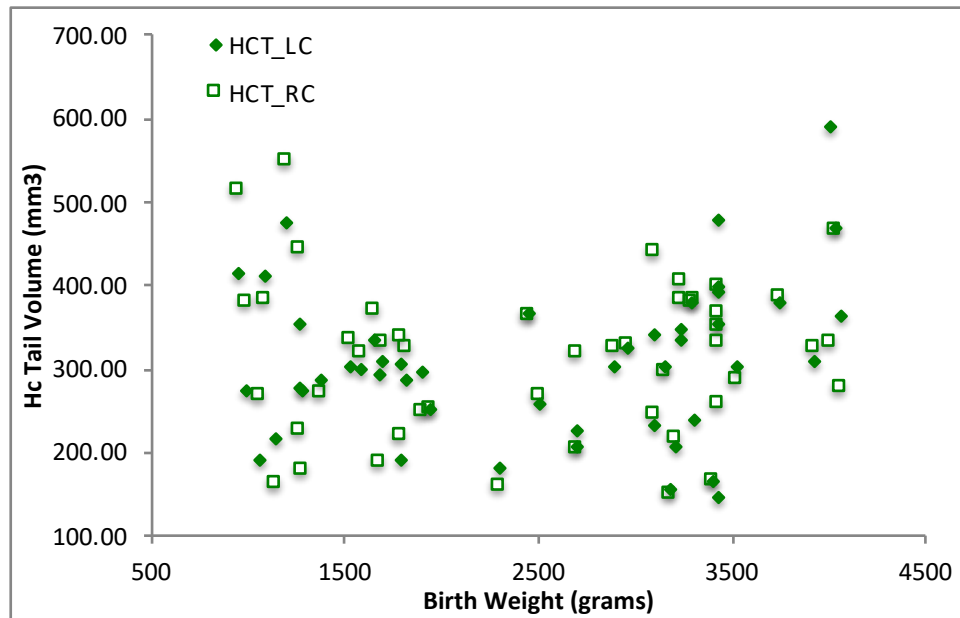
Task	Standard <sup>^</sup>	Input Modality	Study Phase			Test Phase			Interfere <sup>+</sup>	Association
			Individual Stimuli	Simultaneous Stimuli	Delay	Individual Stimuli	Simultaneous Stimuli			
CVLT-C Total Recall*	X	Auditory		X			X		--	
Picture-Pair item test*		Visual		X	X		X		--	
Picture-Pair pair test*		Visual		X	X		X	X	Stimuli with each other	
Object Memory old/new within*		Visual	X		X		X		--	
Object Memory old/new across*		Visual	X		X		X		--	
Zoo Locations <sup>+</sup>	X	Visual		X			X		Content and location	
Picture Memory <sup>+</sup>	X	Visual		X			X	X	Stimuli with each other	
Picture Sequencing <sup>+</sup>	X	Visual and Auditory		X			X		Content and location	
Object Memory 2AFC within		Visual	X		X		X	X	--	
Object Memory 2AFC across		Visual	X		X		X	X	--	

Note: \*/Green text = tasks that loaded onto the Memory Factor; +/Red text = the tasks that loaded onto the Low EF factor; Blue = tasks that loaded onto the High EF Factor.

<sup>^</sup>Standardized tasks that can be compared to other children of the same age; raw scores were used for these tasks.

<sup>+</sup>Interference is defined as the simultaneous presence of foil item(s) with target item(s)



**Appendix D: The relationship between corrected Hc tail volume and birth weight**

Although Hc tail volumes were not related to birth weight, we include this figure here to showcase that there is potential for a nonlinear relationship, which was not assessed due to low power.

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**ABSTRACT****HIPPOCAMPAL VOLUMETRY AND EPISODIC MEMORY IN PRETERM BORN CHILDREN**

by

**DANA M. MCCALL****August 2019****Advisor:** Dr. Noa Ofen**Major:** Psychology (Clinical)**Degree:** Doctorate of Philosophy

**Objective** The hippocampus (Hc) is essential for memory and vulnerable to the sequelae of premature birth. Relationships between subcomponents of the Hc and memory performance have been documented in adults. Yet little is known about the generalization of these findings to young children, whether term or preterm-born. This tripartite investigation focused on Hc subregion and subfield volumes, a potential latent construct for episodic memory, and the relationship between Hc volume and memory performance across birth weight (BW) and gestational age (GA).

**Participants and Methods** Forty-eight children (20 preterm), ages 5-7, completed an MRI scan and several episodic memory tasks. An additional 18 children (13 preterm) completed the memory tasks but did not undergo an MRI. Manual demarcation was completed with high reliability for total Hc, Hc subregion, and Hc subfield volumes. A factor analysis was conducted to form a latent construct for episodic memory. Bivariate correlations and general linear modeling analyses were used to evaluate volume-performance relationships.

**Results** Preterm-born children had significantly larger Hc Head volume than term born children. No other significant associations were observed between GA or BW and Hc

subcomponents. Factor analysis yielded a three-factor structure, including a factor we termed episodic memory. Factor scores did not correlate with BW or GA. The episodic memory factor significantly related to Hc Body, Dentate Gyrus, and Subiculum volumes in the whole MRI sample.

**Conclusions** The significant effect in the Hc Head may partially be due to the unique vulnerability of the Hc subregion CA1, which is relatively more largely represented in the Hc Head than the Hc Body. Although we provide limited evidence for differences in regional volumes between term and preterm-born children at this age, our findings do support the notion that specific relationships between Hc volume and memory are present in young children.

**AUTOBIOGRAPHICAL STATEMENT**

Dana is a sixth year Clinical Psychology student at Wayne State University. She has accumulated comprehensive clinical experience, research, and coursework as part of her work towards a PhD in Clinical Psychology. Specifically, she has completed psychological assessments and psychotherapy with adults and children in both medical and private practice settings. Dana is currently completing her Clinical Internship at Children's Hospital of Minnesota and plans to become a pediatric neuropsychologist in a children's hospital or academic medical center following the completion of her degree. Dana is from a small town in Iowa and values spending time and playing board games with family and friends.