TRADITIONAL AND NOVEL HIPPOCAMPALLY MEDIATED COGNITIVE TASKS IN TYPICALLY AND ATYPICALLY DEVELOPING YOUTH

by

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DEDICATION

This dissertation is dedicated to my parents Katy and Terry, both teachers, who are endlessly kind, loving and supportive and who inspired in me a lifelong love of learning.

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ABSTRACT

The hippocampus is known to help in the recall of associations and episodes from the past. This is a form of mental representation, and other forms of mental representation may be associated with the hippocampus as well. Five candidate complex cognitive functions involving suspected hippocampal involvement are discussed in the theoretical part of this dissertation, and a case is made for integration of the hippocampus into developmental theory. As the hippocampus is a gradually developing structure, we must consider how its slow course affects the development of cognitive functions that seem to involve it, at various stages.

Following on this call to update developmental theory with integration of the hippocampus to account for a broad range of representational cognitive processes in Chapter 2, I introduce preliminary models in Chapter 3 in which I seek to test this for the case of creativity. Forty-three youth participated in cognitive data collection (21 with Down syndrome), and 38 of these participants (18 with Down syndrome) also underwent MR imaging. In modeling creativity as a function of memory and executive control, I seek to discover the extent to which memory contributes to creativity. Significant results were found for the group with Down syndrome, with associative memory and executive function emerging as predictors of creative performance. Surprisingly, these associations were absent in the typically developing group, for which the model and the variables were not significant. I also predicted that creativity and adaptive behavior would be positively correlated as representational functions that seem to have mnemonic contributions. Results included a positive correlation for creativity and adaptive behavior in the group with Down syndrome, while these functions were negatively correlated in the typically developing sample.

In Chapter 4 I turn to examining the hippocampus itself. Previous studies have examined the hippocampus at the level of its subfields in adults with Down syndrome but not in youth, and

while automated segmentation studies have been done with typically developing youth, there is little information on whether automated and manual methods agree for this age group. In the current study, subfield segmentations were made for youth with Down syndrome and typically developing youth using both methods in order to determine what group differences characterize the development of subfields, how well the methods concur with typical and atypical samples, and whether specific subfields relate to specific cognitive functions. The two methods showed small to moderate correlations across the subfields tested. The anterior hippocampus was correlated with associative memory in both groups and the CA1 subfield with adaptive behavior in both groups. Creativity did not show a correlation with hippocampal subfield volumes.

Altogether group differences were more profound than expected in the studies described in chapters 3 and 4. Creativity, putatively linked to the hippocampus in Chapter 3, was well described by memory and executive control in the DS sample only. Possible explanations for this difference and the directionality difference between groups in the creativity to adaptive behavior study are offered. In Chapter 4, volumetric results largely supported hypotheses, but the methods produced less similar segmentations than anticipated, suggesting that continued caution is warranted in using automated methods with youth and special populations. Memory was similarly correlated with anterior hippocampus in both groups, but CA1 was only significantly related to CA1 in the DS group after correction, and creativity as a whole bore no significant relationships to subfields, although the creativity domain of flexibility was significantly related to CA and DG subfields in typically developing youth.

In total, this dissertation explored hippocampal development and the concurrent development of "hippocampal" representational skills. More work is needed in order to understand how the developing hippocampal subfields interact with other brain regions and

networks, how this changes across developmental time and how it may differ in various models of hippocampal impairment.

CHAPTER 1
INTRODUCTION

Since its identification with explicit memory processes through the study of H.M., the hippocampus has been consistently studied in this role. The hippocampus allows us to bind information into a cohesive memory, making it a fundamental neural substrate in associative memory formation (e.g., Burgess et al., 2002; Davachi & Wagner, 2002; Yonelinas et al., 2001). It is also active in memory recall (e.g., Wiltgen et al., 2010), a process that I will propose as fundamental to the complex cognitive functions described in this dissertation. Because the hippocampus is an allocortical region with an extended path of postnatal development, this development may be examined in neurotypical populations and populations with known hippocampal dysfunction to understand differences in the development of its functionality, its subfields and its connections with other brain regions. In this dissertation, I present a call for the hippocampus and its extended development to be integrated into existing developmental theory, examine complex cognitive processes reliant on the hippocampus and present a cross-sectional study of the hippocampal formation in typically developing youth and youth with hippocampal dysfunction, specifically, Down syndrome (DS).

Neuroconstructivist theories of development emphasize the brain's growing capacity to form mental representations (Piaget, 1954; Johnson, 2001; Karmiloff-Smith, 1990). Memories are a form of mental representation, as they are no longer attached to present-moment stimuli when they are recalled (or more accurately, reconstructed). The hippocampus supports representation through its involvement in memory consolidation and recall, and also engages with other brain regions structurally and functionally to interactively support complex representational and cognitive skills. Representational cognitive processes that involve hippocampal activity have the potential to provide insight into the day-to-day utility of hippocampal function, particularly when studied in neurotypical development and models of

developmental hippocampal deficit. A palette of such representational capacities is discussed in the theoretical paper that comprises Chapter Two of this dissertation.

In Chapter Three, two of the complex cognitive processes identified in the previous chapter that I focus on in this context are creative cognition and adaptive behavior. These are cognitive functions that rely on the recall of episodic memory, and thus may also relate to the development of memory and of the hippocampal formation. Creativity, a complex cognitive function that has been found to draw on memory, is defined in the research literature as the creation of ideas or products that are both unique and beneficial (Abraham, 2018). While the skills that go into creative idea production may be diverse, one important component seems to be the recall of stored memories. Memories of situations comparable to the present can aid in the production of fitting creative solutions (as reviewed in Benedek et al., 2023). Adaptive behavior refers to conceptual, social and practical life skills that people utilize to achieve goal-directed behavior in their daily lives (Schalock, Luckasson & Tassé, 2021). For example, independent living skills such as grocery shopping, budgeting, and caring for the home comprise one domain of adaptive behaviors. Adaptive behavior is often measured in intellectual disability (ID) as it is, along with deficits in IQ, a diagnostic criterion (Schalock, Luckasson & Tassé (2021). Adaptive behaviors are likely to involve commitment of an adaptation to memory for future use, as well as the recall, evaluation and reconsolidation of previously tried adaptive skills as needed.

The non-traditional hippocampal functions at the heart of this dissertation (creativity, adaptive behavior) may be differentially affected in cognitive disorders that specifically entail hippocampal impairment (e.g., DS). DS is a condition that arises due to a triplication of human chromosome 21 (Lejeune, Gautier, & Turpin, 1959). It is the most common intellectual disability of genetic etiology, with a prevalence rate of about one per 700 live births (Parker et al., 2010). Individuals born with DS tend to present with deficits in verbal explicit memory, although they

may have somewhat spared non-verbal and implicit learning skills (Godfrey et al., 2018). People with DS generally also have smaller total brain volumes in childhood and adulthood than typically developing individuals (e.g., Pinter et al., 2001). When this difference is corrected for, the ratio of hippocampal volume to total brain volume is still smaller in persons with DS than in controls (Pinter et al., 2001; Aylward et al., 1999; Lovos et al., 2023).

The cognitive phenotype associated with DS is consistent with what is known about hippocampal developmental lags and underdevelopment in this population. An array of hippocampally mediated learning and memory impairments have been well documented in the literature on DS (Fidler and Nadel, 2007; Pennington et al., 2003; Edgin et al., 2012). Beyond general intellectual delays, mouse models and human studies have provided evidence that this condition is associated with specifically hippocampal tasks such as spatial memory, object and place associations, and episodic recall, as well as verbal recall and temporal ordering. Clark et al. (2017) found that individuals with DS showed typical performance for short-term isolated object or configural recall, but impairments in spatial memory, which is consistent with the delayed memory for spatial locations seen in hippocampally lesioned rhesus macaques (Blue, Kazama & Bachevalier, 2013). Lavenex et al. also noted that deficits arise specifically on allocentric spatial memory tasks for individuals with DS compared to mentally age-matched children of typical development (Lavenex et al., 2015; Banta Lavenex & Lavenex, 2021). Impaired verbal short-term memory has of course been found associated with DS (Jarrold & Baddeley, 1997; Raitano Lee et al., 2010). Impaired memory for temporal order of patterns has also been demonstrated in children and adults with DS (Clark et al., 2017). However, little is known about how people with Down syndrome may function on the hippocampally mediated functional tasks of adaptive behavior and creativity in connection with hippocampal development. Down syndrome (DS) provides a useful model for study of hippocampal functions as the trajectory of hippocampal

development in DS may be more gradual than in typical development, allowing for a somewhat more isolated examination of each associated cognitive function (Rast & Meltzoff, 1995; Edgin, 2013).

To help elucidate what impacted neurodevelopmental processes might account for the volumetric differences noted in the hippocampi of individuals with DS, a small body of previous work has examined hippocampal development in DS at the cellular and molecular levels. Impaired neurogenesis has been found in the hippocampal dentate gyrus and cornu ammonis (CA) subfields (Guidi et al., 2008) and in the dentate gyrus and the germinal matrix of the lateral ventricle in infants, children, and middle-aged adults with DS (Contestabile et al., 2007; Wisniewski et al., 1984). The brains of individuals with DS have also been found to have fewer dendritic spines in the hippocampus than age-matched controls (Ferrer & Gullotta, 1990; Suetsugu & Mehraein, 1980) with differently shaped spines (Haas et al., 2013). Furthermore, myelination has been found to proceed at a delayed pace in children with DS, particularly in the trisynaptic circuit of the hippocampus (Ábrahám et al., 2012; Wisniewski, 1990). A smaller density of myelinated axons was also observed in the hilar region of the dentate gyrus in postnatal and adult hippocampi in this population (Ábrahám et al., 2012), indicating impaired efferent fibers from the septum pellucidum to the dentate gyrus of the hippocampus. Impairment of these connections may contribute to decreased ability to encode memories (Ábrahám et al., 2012). Connectivity differences in models of DS have also recently been noted between the dentate gyrus and CA3 networks in the Tc1 mouse model (Witton et al., 2015) and specifically in CA3 associative connections (Hanson et al., 2007). Finally, at least one study has found evidence that the reduced volume and reduced neuron counts found in the DS hippocampus may also be related to increased postnatal apoptosis as well as reduced neurogenesis (Guidi et al., 2008).

Thus, in both human and rodent models of DS, the hippocampus and specifically the dentate gyrus region of the hippocampus is indicated as particularly compromised.

In this dissertation, I present a proposal as to mnemonic and hippocampal contributions to the non-traditional "hippocampal" functions of creativity and adaptive behavior in both typical and atypical development. This analysis is important for characterizing the course and nature of the hippocampal role across development. The hippocampus is considered important (for at least some period of time) to recall as well as to the initial consolidation of detailed memories (e.g., Wiltgen et al., 2010; Moscovitch et al., 2006; Squire, Stark & Clark, 2004). Given the important role of the hippocampus in recall and recombination as well as the known importance of Down syndrome as a model of altered hippocampal development, I first present a theoretical paper in which I discuss how and why the hippocampus may be seen as an important driver of the development of representational capacity in populations with neurodevelopmental disorder. In this paper we call for revisions of theory regarding the processes driving higher level cognitive attainment and impairments therein in ID, all in light of new data regarding the ways in which cognitive representations may be structured and utilized by the hippocampus. Secondly, I examine creativity behaviorally alongside adaptive behavior and more traditional measures of hippocampal function in typical and atypically developing youth in the 11-21 age range. In the final study, hippocampal and extra-hippocampal medial temporal lobe volumes are analyzed cross-sectionally in typically developing youth and youth with DS in the same age range. All chapters include discussions of both typically developing and atypically developing youth (specifically, youth with Down syndrome).

CHAPTER 2

COGNITIVE DEVELOPMENT IN THE CONTEXT OF HIPPOCAMPAL REPRESENTATION

This theoretical paper is under review (accepted for revise/resubmit) at the Trends in Cognitive Sciences *journal. For the full paper, see Appendix A. The abstract is included below after a short introduction.*

This paper brings a theoretical focus to the hippocampus as an important but heretofore largely neglected driver of representational capacities. As indicated above, herein we are focused on neuroconstructivist theories of development. This group of related theories of development emphasizes experience-dependent plastic development as an important part of the development of representational capacities (Piaget, 1954; Johnson, 2001; Karmiloff-Smith, 1990). Prominent among this group of theories is the theory of interactive specialization, which seeks to explain cognitive development through the process of brain regions learning to cooperate with each other to achieve productive and efficient networks that support complex behaviors (Kiani et al., 2022).

Memories are a form of mental representation, as they are no longer attached to present-moment stimuli when they are recalled (or more accurately, reconstructed). The hippocampus supports representation through its involvement in memory consolidation and recall (Karmiloff-Smith, 1990). It also engages with other brain regions structurally and functionally to interactively support complex representational and cognitive skills (e.g. Benedek et al., 2023; Madore & Schacter, 2016; Ellis et al., 2021). Representational cognitive processes that involve hippocampal activity have the potential to provide insight into the day-to-day utility of hippocampal function, particularly when studied in neurotypical development and models of developmental hippocampal deficit. A palette of such representational capacities is discussed in this theoretical paper..

We note that the role of the hippocampus has already been incorporated into theories of learning through the Complementary Learning Systems Theory (CLS), which suggests

complementary roles for the hippocampus and frontal lobes in supporting learning (Kumaran, 2016). We propose that the hippocampus should likewise be integrated into theories of cognitive development and theories of ID as an important complementary region to the frontal lobe that currently dominates the theories.

There are a handful of representational higher cognitive functions we point to in which evidence of hippocampal involvement can be seen. Creativity, future imagining, prediction, exploration, curiosity, and statistical learning are all representational functions of the human brain that evidence hippocampal neural correlates. Finally, we discuss what this may mean for individuals with a variety of neurodevelopmental disorders including Down syndrome, autism spectrum disorder, Williams syndrome, Fragile X syndrome, and learning disabilities.

The full paper is included as Appendix 2.

Abstract

Neuroconstructivist theories of development incorporate an understanding of brain plasticity and connectivity but have yet to fully consider a role for the hippocampus as a connected region helping to shape interactive developmental processes. Accumulating neuroscientific evidence regarding hippocampal representation from the research fields of creativity, curiosity, prediction, exploration, and statistical learning indicates the hippocampus as a dynamic and interactive representational structure that must be considered an important player in development and disorders of development. We discuss the role of the hippocampus in cognitive development and disorders in the context of neuroscientific evidence for hippocampal representation.

CHAPTER 3

A BEHAVIORAL STUDY OF TRADITIONAL AND NON-TRADITIONAL MEMORY-DEPENDENT COMPLEX COGNITIVE FUNCTIONS

Author Note

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Abstract

In DS, creativity during development could have real-world benefits. The new MemiC framework for creative cognition links both types of explicit memory as well as prefrontal executive processes to creativity. If this is true, we should be able to see support for this association in our data. We asked adolescents with the DS model of hippocampal impairment and typically developing (TD) youth to participate in verbal and nonverbal divergent thinking tasks in the lab, and their parents filled out behavioral questionnaires. Twenty-three youth with DS and 22 TD youth participated in this study of memory and memory correlates. In this study I build stepwise generalized linear models to account for relative contributions of memory and executive function to creativity in each group and use a Pearson correlation to examine whether creativity bears a positive association with another complex cognitive function: adaptive behavior. The only CAP domain with no groups difference was fluency, $t(18) = 3.29$, p=.29. The full model fit best for the DS group with an R^2 of 0.64, and significant associations with combined creativity were found for associative memory, $t(18) = 3.34$, p=.02 and the behavioral regulation index of the executive control questionnaire, $t(18) = 4.89$, p=.008. The TD model was not significant, $R^2 = 0.27$. Adaptive behavior was positively correlated with creativity for youth with DS, $r(20) = .49$, $p = .048$ but negatively for the TD group, $r(15) = -.68$, $p = -.007$. Altogether, youth with DS demonstrated as much capacity (fluency) for creative production as did TD youth, but not the flexibility, elaborative skill, or verbal aspects of creativity. Both associative memory and one component of executive control were significantly associated with creativity in the DS model only, but curiously, not for the group with TD. Associations between creativity and adaptive behavior also differed by group and the positive correlation in the group with DS was driven by the communication domain of the adaptive behavior scales.

Introduction

Explicit memory is important in its own right, and also in its contributions to complex cognitive functions that rely on information recall. Following on a great deal of work in the creativity field, notably including the Schachter lab's episodic induction studies (Madore et al., 2014 & 2016), creativity stands out as one such cognitive function. Recently creativity has been understood to involve both types of explicit memory (semantic or factual, and episodic or personal) and their neural substrates (as detailed in Benedek et al., 2023). In the research literature, creativity was historically thought to rely more heavily on executive function and the frontal lobes than explicit memory and the medial temporal lobes, as is also the case for adaptive behavior (the sum of skills that people use to function in the necessary realms of their daily lives in order to achieve goals) (AAIDD.org). In this chapter I make a case for the involvement of episodic memory in complex cognitive representational tasks that are likely to involve processes of recall, integration, and novel recombination; and I make a study of creativity and adaptive behavior as two such functions.

Creativity is important to a broad swathe of human spheres including science, design, innovation, mental health, and every-day problem-solving, as well as artistic endeavors. Immersion in creative activities is also used to help adults and children move therapeutically through trauma and to process grief and anxiety (as reviewed in Leckey, 2011). Creativity researchers understand a creative process to entail internal attention in service of a generative goal (Green et al., 2023), and creative output to have two primary components: originality (novelty) and appropriateness (usefulness within a given context) (Runco & Jaeger, 2012). In other words, a creative offering has an element of originality in content and also offers something uniquely useful within the context of the problem to be solved or space to be artistically treated.

The longstanding associative theory of creativity (Mednick, 1962) assumed that creative ideation comes about through executive processes and some amount of semantic memory activation and recombination of remembered elements in unique and fitting ways. In contrast, the newly developed and more detailed MemiC framework (based on recent cognitive and neuroimaging evidence) holds that creative cognition involves both semantic and episodic memory, recruited across different stages of the creative process (Benedek et al., 2023). In the MemiC framework, creative output is thought to include both memory retrieval and memory construction along with the more prefrontally-mediated evaluation of candidate ideas (Benedek et al., 2023). Creative idea construction as a process is thought to occur in four stages in this theory. The first two of the four stages of creative ideation in the MemiC framework are generative and are thought of as a "search" phase and a "construction" phase. These early two phases are thought to include searching and constructing ideas from both episodic and semantic memory, allowing memory a larger share in creative ideation than previously acknowledged. The third and fourth stages, both evaluative, are thought of as "novelty evaluation" and "effectiveness evaluation" respectively. The evaluative stages are thought to call on prefrontal resources more than medial temporal lobe. In this framework, all four stages are thought to be iterative (Benedek et al., 2023).

In terms of neural correlates, creativity seems to draw on a few known brain networks that include profrontal and medial temporal lobe activity. (Beaty et al., 2016; Beaty et al., 2015; Ellamil et al., 2011). Beaty et al. (2015) collected fMRI scans of 25 young adults performing a creativity task while in the scanner. They conclude that default mode, executive control, and salience brain networks coordinate the activities of spontaneous thought, cognitive control, and semantic memory retrieval in support of creative idea generation (Beaty et al., 2015). A recent fMRI-guided transcranial magnetic stimulation study indicates a particular role for episodic

memory search in creative activity. Recently, Thakral et al. used selective disruption of a hippocampal network at the left angular gyrus with continuous theta-burst stimulation to demonstrate reduced fluency of both episodic details and idea production while the targeted network was disrupted (2020), showing support for hippocampal involvement in creative processes.

Creativity during development can now be viewed with an eye toward contributions of both memory and executive functions as tandem gradually-developing cognitive functions. These functions may mediate creative processes differently at different stages of hippocampal and frontal lobe development. As many youth with DS have verbal deficits, the one previous study (De Caroli and Sagone, 2014) and the current study both primarily use a non-verbal creativity task (Williams, 1975). The previous study of children with DS (6-10 years old) found that when compared to cognitive age-matched controls, children with DS performed similarly in non-verbal creative tasks, but significantly lower on tasks involving verbal production (De Caroli and Sagone, 2014).

A similar cognitive and neural signature is suspected of the group of skills known collectively as adaptive behavior. Following on the 2007 theoretical review by Bast chronicling the integrative capacity of the hippocampus and how this provides ideal support for adaptive behavior, adaptive behavior scales are also considered in this chapter. Adaptive behavior refers to the set of practical, conceptual, and social skills of daily living that enable a person to attain their most independent lifestyle possible. Adaptive behavior is generally understood to encompass three areas of skill: conceptual (including reading, managing time and money, etcetera), as well as social and practical life skills (AAIDD.org). Adaptive behaviors are particularly utilized by and meaningful to persons with intellectual and/or physical disabilities. For example, persons with DS who have difficulty producing clear speech may have limited communication reflected

in lower adaptive behavior communication scores, or in some cases may utilize sign language and/or digital assistants for communicating successfully, reaching wider audiences than they would otherwise be able to reach and bolstering their adaptive communication skills. Adaptive behavior gains can manifest in activities of daily living (ADLs) such as personal care and household chores capacities, social and communication skills, as well as employment in adulthood or even the teenage years.

During development, early adaptive behaviors begin to emerge as self-care responsibilities, such as dressing, toileting and grooming. Social and community adaptive skills follow. Thus, the development of adaptive behaviors usually translates into greater independence. Adaptive behavior and intelligence quotient together make up the two aspects of the diagnostic criteria for intellectual and developmental disabilities.

Previous research has sought to explain adaptive behavior through exploring its relationship with executive control and its prefrontal lobe neural underpinnings (e.g., Koechlin, 2016; Collins & Koechlin, 2012; Ridderinkhof, Band, & Logan, 1999). In one prior study, Onnivello and colleagues found correlations across domains between executive functions and adaptive behaviors in school-age children, indicating the importance of executive function in daily living (2022). In contrast, a previous study of children with DS indicated a relationship between spatial associative memory and adaptive behavior (Edgin et al., 2010), while a study of autistic young adults similarly found that greater memory difficulties correlated with poorer adaptive skills (Godfrey et al, 2023). Much like creativity, adaptive behavior may be dependent on recalling previous scenarios from memory and recombining that information with current, context-relevant information to achieve a successful outcome. This part of the dissertation will theoretically present and discuss why behavioral adaptation may be dependent upon hippocampally-mediated functions and the hippocampus as much as or more than prefrontal

lobe-mediated functions or the prefrontal lobes. This consideration is important in understanding the full, broad scope of hippocampal contributions to behavior and could help highlight the need for the development of hippocampally-focused interventions in the future.

Individuals with DS present a model of developmental episodic memory impairment, leading to the question of whether cognitive functions dependent on memory input might be spared, impaired, or adapted and how the neural signatures of creative ideation and adaptive behavior manifest in this population. Furthermore, as two cognitive functions that might be driven partially by cognitive control and also episodic memory, what will the relative contributions of memory and executive functions each be?

Examining memory performance alongside such complex cognitive functions as creativity and adaptive skills could help indicate how well memory performance scores translate into effective real-world behavior in the course of both typical and hippocampally impaired development. The current study offers a new model of creative cognitive that accounts for both mnemonic and control processes, as indicated by the MemiC framework. A correlational study is then made between creativity and adaptive behavior, as two cognitive functions both indicated to bear relationships with executive function by some studies, and to memory in others, as detailed above.

Specifically, this study is designed to answer the following questions:

RQ1: What is the cognitive relationship between creativity (combined verbal and non-verbal) and other cognitive functions during the teenage years, and will it differ between groups?

H1a: Modeling creativity as a function of memory and executive function will demonstrate that both together comprise the best model for creativity according to previous research and current theoretical work. Group differences in the relative contributions of memory and

executive function to creativity are expected, with memory contributing less toward creativity scores in the DS group than in the TD group.

H1b. In the group with DS, creativity scores may be more mediated by sematic knowledge in lieu of full hippocampal function and in the presence of lower memory performance.

RQ2: Does being creative confer on youth a capacity for more or greater adaptive behaviors?

H2a: More creative youth will exhibit higher adaptive behavior composite scores, with potential group differences in the magnitude of correlation.

This research is novel as in the wake of new theoretical advances, this project is the first to combine cognitive control and memory in modeling complex cognitions across this span of development in these two groups. This research is important to people's lives as it could indicate that creativity might be further explored as a pedagogical device in the education of youth with DS. Finally, this study also aims to examine whether creativity confers any benefit to adaptive behavior in either group.

Methods

Participants

Forty-five youth between the ages of eleven and twenty-one participated in this study. Twenty-three youth with DS (M = 16.4, SD =3.7) and 22 typically developing (TD) youth (M = 16.2, SD = 3.4) completed the study (see Table 1 for full demographic characteristics). For those in the group with DS, diagnosis of DS was confirmed via physician report of karyotype. Study demographics are reported in Table 1 below. Exclusion criteria included prior head trauma as well as insufficient ability among the youth with DS to communicate. This was assessed via the ability to verbally assent to the study procedure and a demonstrated ability to follow training instructions.

Table 1
Demographics.

Group	*n*	Age	Sex	Sex χ^2	Ethnicity			
					White	Hispanic	African-American	Ethnicity χ^2
DS	23	16.7(3.7)	12 M	χ^2=1.13	13 (62%)	8 (38%)	0 (0%)	χ^2=4.06
TD	22	16.2(3.4)	9 M	*p*=0.29	18 (82%)	3 (13.5%)	1 (4.5%)	*p*=0.37

Participants were recruited through rosters from previous studies, at local events, and through state-wide and national posts on DS social media and lists. All aspects of the study were approved by the University of Arizona Institutional Review Board.

A power analysis was undertaken to test group differences on the cognitive measures included in Chapter 2 of this dissertation. With an effect size from a previous associative memory study of *d*=.74 (Edgin et al., 2010), sample sizes of *n*=23 each and a significance level of 0.05, this study achieves a power of 0.69. Although this indicates that the current study is underpowered, these data were collected as part of a neuroimaging study of youth with DS, for whom recruiting is an arduous task with the current study size representing one of the largest neuroimaging studies of this population to date. Efforts were additionally made to recruit participants for the cognitive study only, resulting in an additional six participants.

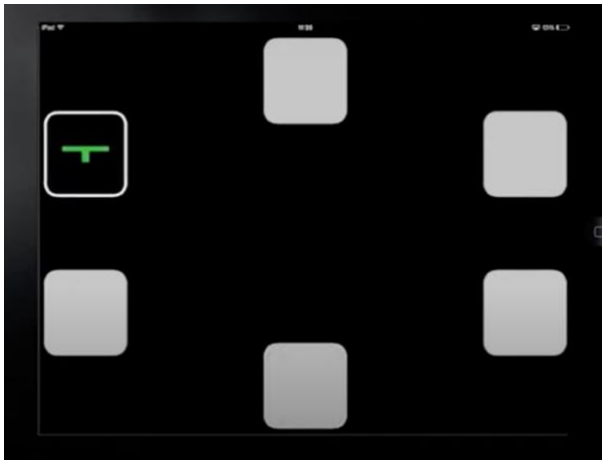
Materials

Cantab-PAL Online Associative Memory Game.

Each participant completed an online version of the Cantab-PAL (paired associates learning) test (Cambridge Cognition, 2012) from their home. The online module first provides instructions for completing the task, and participants are instructed to watch the cards in each round. Each round begins with the cards arranged along the edges of the screen. One by one, the cards are turned over to reveal either a blank or a pattern (see Figure 1 below). After one second, each card is hidden again before the next is revealed. After all cards are revealed and subsequently hidden, a pattern appears in the center of the screen and the participant must tap the

correct location of its match. The rounds contained sequentially more patterned cards, building up to six. The primary variable of interest is the first attempt memory score (PALFAMS).

Figure 1. Paired Associates Learning.



Sea Hero Quest.

Each participant completed an online small-scale spatial navigation task in order to provide data on episodic spatial memory during development. Nine easy to medium difficulty levels were selected for our use with youth by the Sea Hero Quest game's creators (Spiers et al., 2016). In each level, participants were first shown a map to be viewed for as long as wanted. Once they clicked "play" the map could not be viewed again. Their task was to drive a power boat to each of the buoys shown on the map in correct (sequential) order as quickly as possible in order to collect pictures of sea creatures before they hid underwater (see Figure 2, panels a and b for images of a typical map and a typical game wayfinding environment). The levels contained between two and four buoys. The other two levels contained a different challenge: the participant was asked to navigate through the environment looking for a bright red flare gun. When it was found, they were presented with three trajectories to choose from in order to shoot the flare gun back in toward their starting location (Figure 2 panel c). The primary variable of interest will be length of time navigating the path to each buoy, which has been indicated by Spiers, Coutrot & Hornberger (2021) as the most valuable simple metric to quantify spatial ability. Elapsed time will be used as a measure of spatial episodic memory in this study.

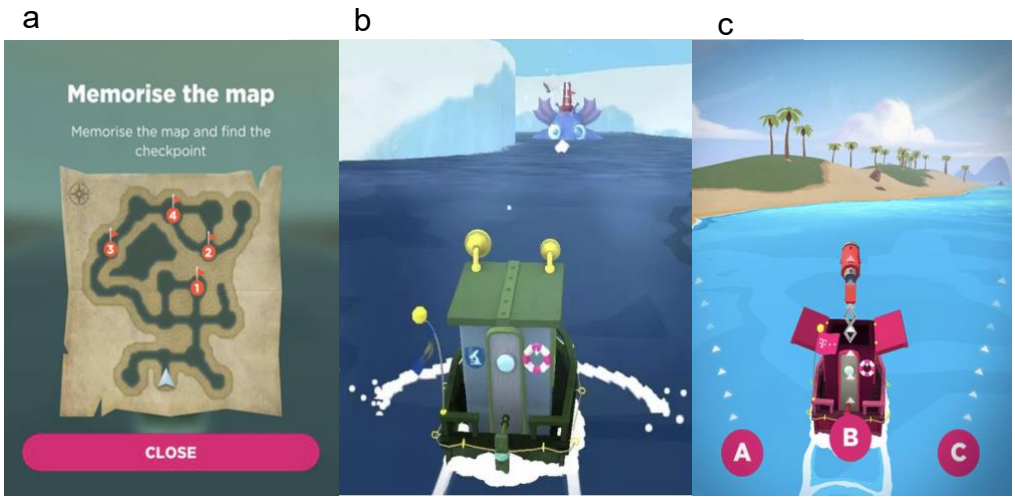


Figure 2. Sea hero Quest Game. A) The map is shown prior to navigation on each level. B) Navigating the boat through a typical fjord level. C) Choosing between 3 possible starting positions on a flare level.

Creativity Assessment Packet (CAP).

Each participant completed a combined non-verbal and verbal assessment of divergent thinking (Williams, 1993). Divergent thinking is a collection of methods for measuring multiple skills involved in creative output, innovation and problem solving (Runco & Pritzker, eds., pg. 60, 2020). The current study's non-verbal drawing task was chosen in order to maximize participation by minimally verbal youth with DS. The task consisted of twelve seed figures, which the participant was instructed to use to create a drawing within the given square (see examples of one participant's drawings in Figure 3). Participants were provided with colored pencils and a pen for writing unique titles under each picture frame. They were assured that the researcher or parent was available for writing out the titles should they choose. Drawings were

scored according to CAP protocol, resulting in scores for fluency, flexibility, originality, elaboration, and title. The first four, as non-verbal measures, may be combined to produce a non-verbal metric, while the fifth may serve as an aspect of verbal measurement.

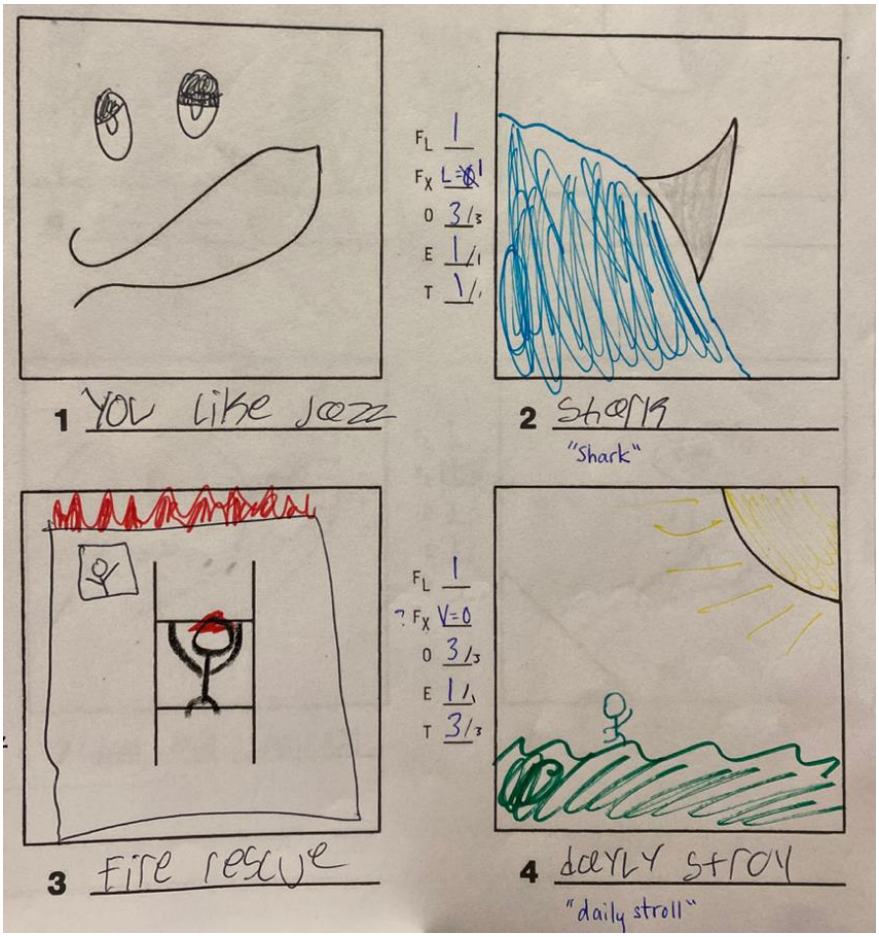


Figure 3. CAP drawings by a 12-year-old boy with DS.

Arizona Memory Assessment for Preschoolers and Special Populations (AMAP) Phase 23.

Each participant completed a short verbal generativity task to complement the non-verbal assessment. Participants had one minute to name all the members of a category (e.g., “fruits”) that they could think of. Participant answers were audio recorded for accuracy. Total words generated, errors and perseverations are utilized as metrics. Additionally, these verbal generativity results as well as the titles from the CAP task may be used to generate semantic distance, a frequently used measure of divergent thinking in creativity studies.

Semantic Distance.

The two verbal measures were both candidates for semantic distance analysis; however, both verbal tasks were constrained by low participation numbers, so the simple semantic distance

analysis from the titles task of the CAP will be analyzed in Appendix 2. Semantic similarity measures were employed such as Path Length Similarity (PATH), summing nodes along the shortest path between the main noun in the titles; and Wu-Palmer Similarity (WUP) to assess the relatedness of depth of a set of titles to assess creative drawing titles on the free platform ws4jdemo.appspot.com.

Vineland-II Adaptive Behavior Scales (VABS-II).

Each parent was asked to fill out several questionnaires on an online HIPAA-compliant research platform. The Vineland-II is included to measure parent-reported adaptive behavior in the five domains of communication, daily living skills, socialization, motor skills, and maladaptive behavior (Sparrow et al., 2005). It is commonly used to evaluate daily functioning, adaptive behavior skills, social development and generally as a necessary component of developmental evaluations. Composite scores are utilized in this study.

The Behavioral Rating Inventory of Executive Function-2 (BRIEF-2).

Each participant's executive skills were assessed via parent report form by a parent or guardian. The BRIEF-2 parent report form was chosen as a measure that would accommodate the wide and widely different ranges of both the typically-developing group and the group of youth with DS. It is commonly utilized in studies of children, adolescents and adults with DS. A previous study has suggested that the parent report form is more accurate for youth than the alternate self-report form and also at least as accurate as in-lab tasks (Riccio et al., 2022). The BRIEF-2 General Executive Composite is included in this study as a measure of executive control, as are its three subcomponent indices, the Behavioral Regulation Index (BRI), the Cognitive Regulation Index (CRI), and the Emotional Regulation Index (ERI).

Kaufman Brief Intelligence Test, Second Edition (KBIT-II).

Each participant's verbal and non-verbal intelligence scores were estimated using the KBIT-II. Raw verbal scores were included in the model.

Data Analysis

Floor and ceiling effects were assessed for all tasks. Variables were transformed if skewed or kurtotic. For the creativity regression models, all variables were transformed into z-scores to provide greater ease in interpretation of the differently scaled measures. Contributions of memory and executive function to combined creativity were assessed with a stepwise regression analysis in order to characterize the pattern of correlation between associative memory, spatial memory, creativity, and executive function for the group with DS and the group with TD separately. Each model began with crystallized semantic knowledge and then associative memory, spatial memory, executive function indices, and sex were sequentially added. Variables were then removed if they did not contribute to a positive change in the model R^2 or a drop in the model RSE. The full models are reported in the results section below.

For the research question regarding adaptive behavior, the variables were checked and found to meet assumptions for a Pearson correlation.

Results

Descriptive data

Demographic sample data. As shown in Table 1, the average age of participating youth was 16.7 years for the DS group and 16.2 for the TD group. The youth were 62% White and 38% Hispanic in the DS group; and 82% White, 14% Hispanic, and 4% African American in the TD group. In the DS group 12 of 23 participants were male, while in the TD group 9 of 22 participants were male.

Descriptive statistics. Descriptive statistics for cognitive measures including means, standard deviations, and group differences are presented in Table 2. Of the creativity measures, fluency alone showed no group differences, $t = 1.23$, p=.29. For all other measures, the TD group had statistically higher group scores. Violin plots of the group results on creativity measures assessed in the CAP are presented in Figure 4. To characterize mean creativity scores by chronologic age across the years of 11-21, CAP ~ Age scatterplots are offered in Figure 5.

Table 2
Descriptive statistics for cognitive measures.

	DS			TD			*t*-Test		
	n	*M*	*SD*	*n*	*M*	*SD*	*t*	*p*	Adj. *p*
KBIT-II verbal*	21	14.72	8.89	21	44.5	6.68	-9.43	<.001	<0.001
Verbal fluency (AMAP 23)	16	6.94	4.09	16	13.92	4.34	-4.36	<.001	<0.001
BRIEF global	24	57.67	11.01	22	50.77	8.6	2.38	.024	0.028
Adaptive Behavior (VABS-II)	21	63.19	12.21	19	105.53	13.2	-9.32	<.001	<0.001
VABS-II soc	19	65.47	11	19	102.6	12.9	-9.05	<.001	<0.001
VABS-II com	19	62.74	16.2	19	97.4	15.4	-6.33	<.001	<0.001
VABS-II dl	19	64.74	16.4	19	114.1	17.3	-8.52	<.001	<0.001
PAL - FAMS	30	8.63	4.94	29	15.76	3.27	-6.55	<.001	<0.001
Titles (CAP)	20	11.6	7.84	17	19.12	5.26	-3.29	<.001	<0.001
NV CAP flexibility	20	59.9	3.84	18	8.56	2.01	-3.62	<.001	<0.001
NV CAP fluency	20	9.9	9.9	17	11	1.77	-1.23	0.23	0.29
NV CAP elaboration	20	8.05	6.59	17	13.81	4.18	-3.19	0.004	0.005
NV CAP originality	20	17.75	9.62	17	7.06	9.36	-3.04	0.004	0.006
SHQ L3	18	81.46	88.88	20	24.49	6.8	2.7	0.002	0.006

** KBIT-II raw scores*

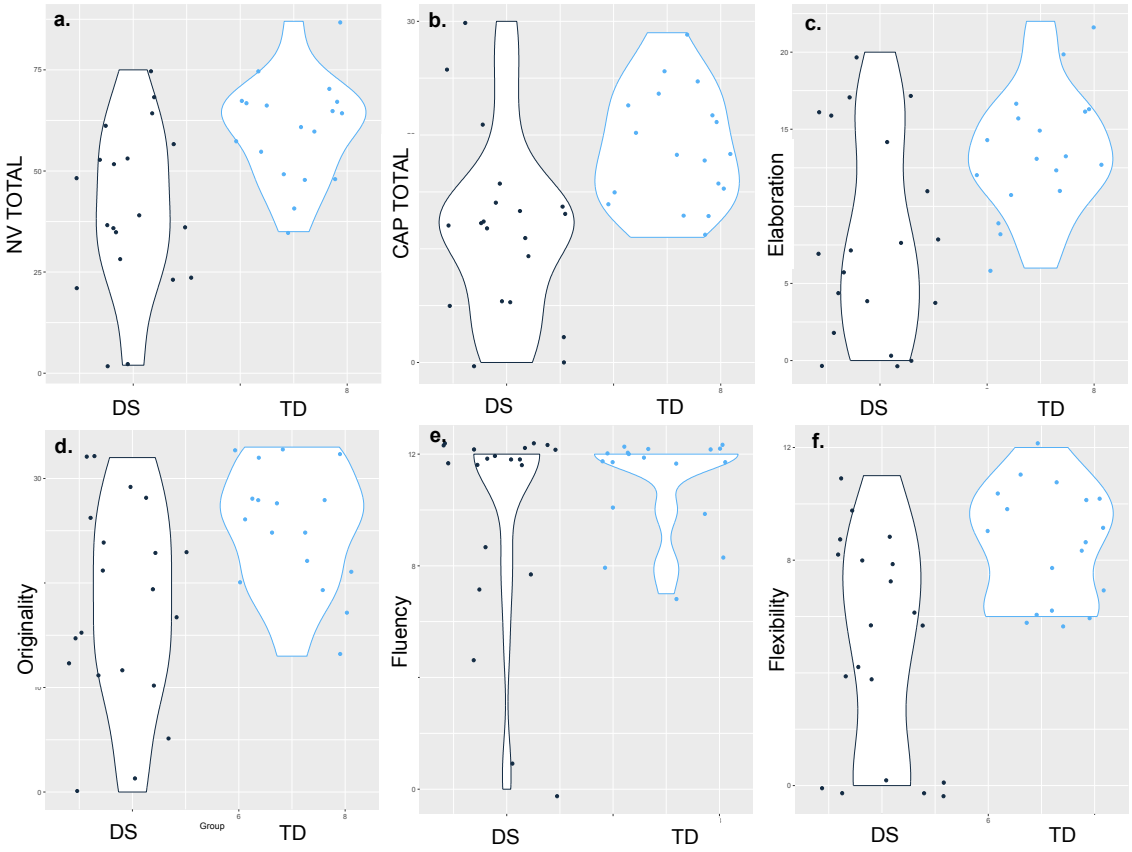


Figure 4. Grouped plots for the CAP domains: a. non-verbal creativity, b. verbal (titles) creativity, c. elaboration, d. originality, e. fluency, f. flexibility.

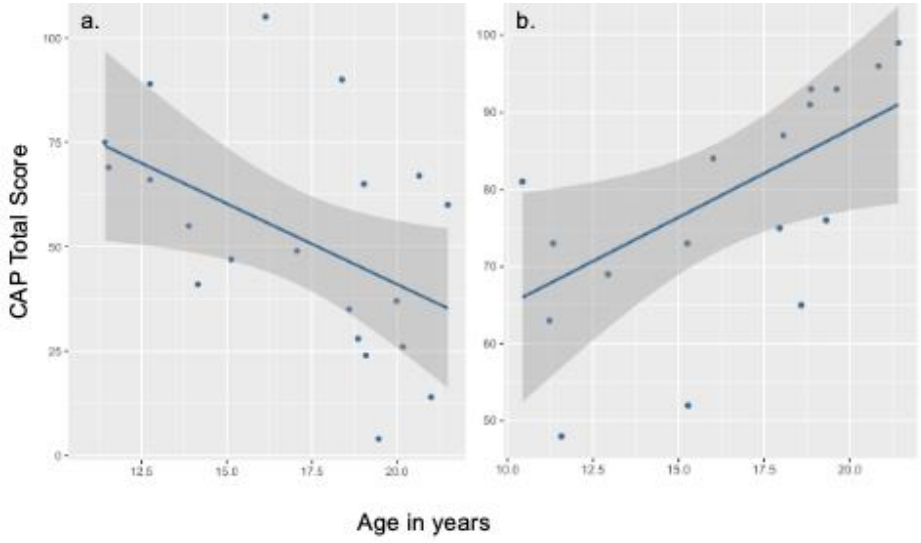


Figure 5. Shaded bands around best-fit lines indicate 95% CI on fitted values for the correlation plotted in a. (left) for youth with DS; and b. (right) for youth with TD.

Statistical Models

For all statistical evaluations the reported *p*-values have been adjusted using the false discovery rate correction.

Creativity.

Stepwise linear models for combined creativity (all verbal plus nonverbal domains of the CAP) were separately constructed for each group. Due to missing data and the inability of some youth with DS to participate in some measures, 19 participants from each group with complete data were included in this analysis. For the group with DS, the best-fitting model contained accumulated verbal semantic knowledge, associative memory, spatial episodic memory, and the cognitive, behavioral and emotional regulation indices from the adaptive behavior scales. The model ($F(6,12) = 7.36$, $p = .009$) had an adjusted R^2 of 0.64 and an RSE of .61. Significant and positive correlations were found for associative memory, $F = 3.70$, $p = .02$, and the behavioral regulation index (BRI), $F = 4.74$, $p = .008$. Details for the full model are included in Table 3 below. For the TD group, the best-fitting model was a reduced model ($F(4,14) = 0.28$, $p = .91$) with an adjusted R^2 of .27 and an RSE of 1.07. No variables were significant. Linear plots of the variables that were significant in the DS group's model are also included for TD participants in Figure 6.

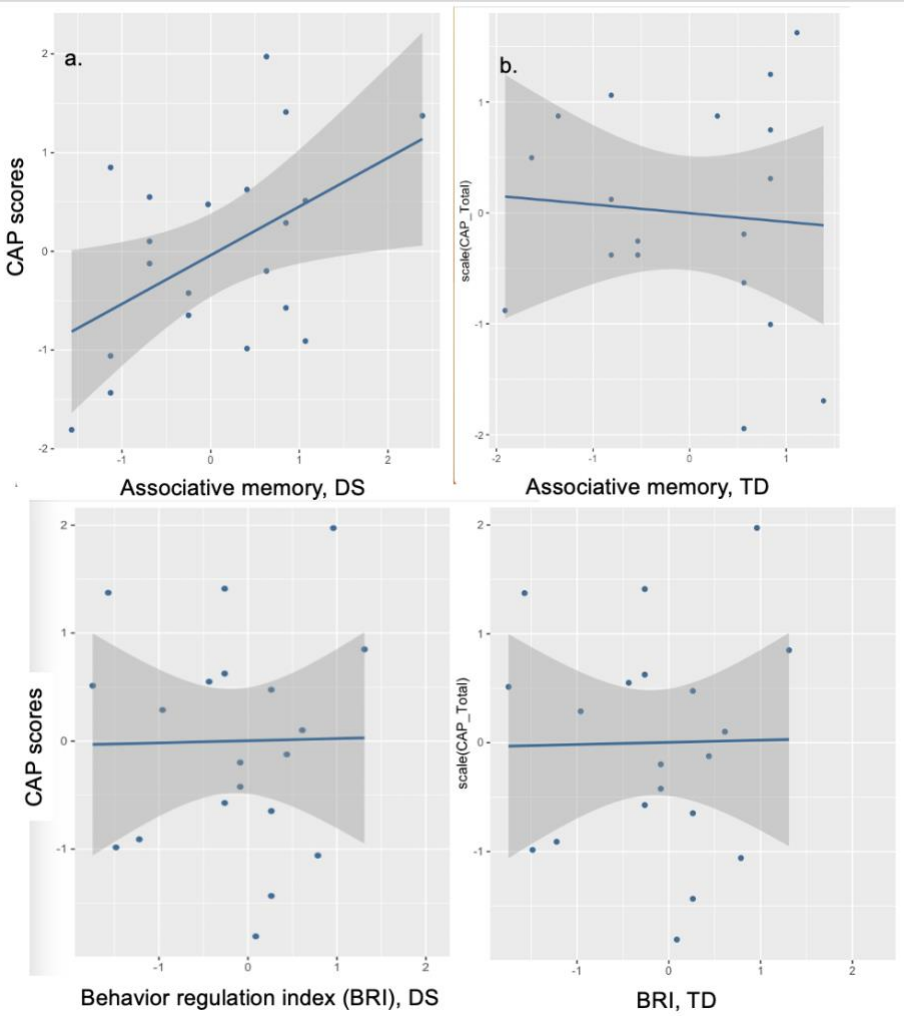


Figure 6. a. Associative memory (PALFAMS) for DS group; b. PALFAMS for TD group; c. behavioral regulation index (BRI) for DS group; d. BRI for TD group.

Table 3
Results of best-fit linear regression modeling the contributions to creativity in youth with DS.

	Coefficients				Model		
	Beta Coeff.	*t*-val.	*p*-val.	Adjusted *p*-value	F-statistic	*p*-value	Adjusted *p*-value
KBIT-II	0.44	1.58	0.16	0.14	5.23	0.008	0.01 **
Sex	0.44	0.91	0.38	0.5			
PALFAMS	0.81	3.31	0.007	0.016 *	Adjusted R^2		
SHQ	-0.22	-1.01	0.34	0.58	0.61		
CRI	-0.54	-1.52	0.15	0.4			
BRI	1.7	4.89	0.0019	0.01 **			
ERI	-0.33	-1.39	0.19	0.4			
Age	0.006	0.11	0.92	0.99			

Adaptive Behavior. Adaptive behavior was found to decrease across the studied age span for both groups, as shown in Figure 7. A correlational study was performed on creativity and adaptive behavior to gather preliminary evidence as to whether more creative youth are also able to demonstrate greater adaptive behavior skills. Due to missing data for some measures, 21 participants from the DS group and 16 in the TD group were included in this analysis.

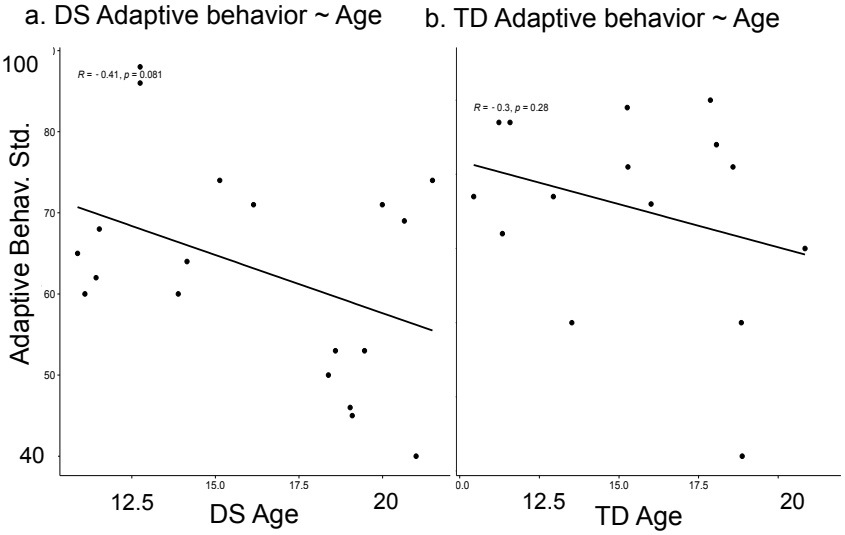


Figure 7. Adaptive behavior composite scores across adolescence.

A modest positive correlation was observed between the adaptive behavior scales and nonverbal creativity for the group with DS, $r(20) = .49$, $p = .048$. For the TD group, a strong negative correlation was found, $r(18) = -.68$, $p = -.007$.

Because of this finding, the component domains of the adaptive behavior scales were also investigated. For the youth with DS, the communication domain was significantly positively correlated with creativity, $r(20) = 2.4$, $p = .03$.The socialization and daily living skills domains were not significant, all $p > .05$. As the communication domain proved significantly positively correlated to creativity for youth with DS, it was then tested in the other group. For TD youth, communication was also correlated with creativity, although the correlation was negative, $r(15) =$

-.58, p = .029. All correlations are reported in Table 4 below, and the significant correlations are plotted in Figure 8 below.

Table 4
Creativity – Vineland Adaptive Behavior (VABS-II) Correlations.

	Rho	*t*	df	*p*	Adjusted *p*	95 % C.I.	
DS - VABS-II Composite	0.48	2.15	20	0.05	0.05*	0.01	0.78
TD - VABS-II Composite	-0.68	-3.24	15	0.007	0.01*	-0.89	-0.24
DS - VABS-II Communication –	0.52	2.4	20	0.03	0.04*	0.05	0.80
TD - VABS-II Communication	-0.58	-2.47	15	0.03	0.04*	-0.85	0.19
VABS-II DS - Socialization	0.33	1.35	20	0.20	0.4	-0.18	0.70
DS - VABS-II Daily Lvng Skills	0.43	1.87	20	0.08	0.3	-0.06	0.76

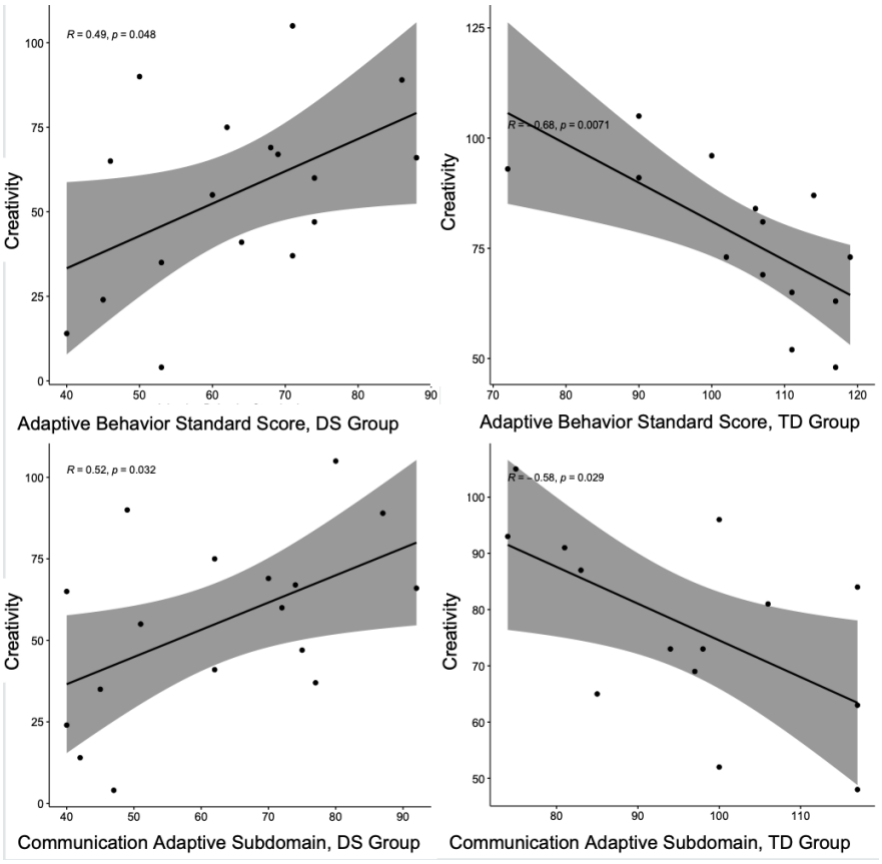


Figure 8. Correlation plot array for creativity and adaptive behavior. The top row shows correlations with the overall adaptive behavior score; the bottom row shows correlations with the communication subdomain of the adaptive scales. DS group to the left; TD group to the right.

Discussion

The stepwise linear models for creativity were constructed to more fully account for the cognitive functions that support creativity by testing new theoretical work in two populations. The models yielded some unexpected differences by group. First, the model fit the data reasonably well in the group with DS as evidenced by the R^2 of 0.61; but the best-fitting model in the group with TD was not a good fit with an adjusted R^2 of 0.27. Additionally, although associative memory and behavioral regulation contributed to creativity in the youth with DS, neither memory nor executive control measures bore connection to creative cognition in the TD model. Perhaps this group difference was influenced by the age interactions with creativity and adaptive behavior. It is possible that some mnemonic functions are active in childhood and in developmental disability that have become more corticalized in typically developing teens of an average age of 16. However, executive functions were also not significant in the model for TD youth, suggesting that this theory is not correct or is at least not the only correct mechanism at play. While it was expected that group differences would arise, it may be possible that the measures utilized were not as suited to assessing cognitive development in the TD sample as they were in the DS sample.

As for the two significant variables found for the group with DS in the current study, each was related to memory in previous literature. In the case of associative memory, this has long been understood to contribute to creativity. Notably, our measure of spatial episodic memory did not emerge as significant. As for the behavioral regulation index (BRI), it was a surprise to see this association rather than an association with the cognitive regulation index (CRI). The BRIEF's BRI consists of the *inhibit* and *self-monitor* scales while the CRI consists of *working memory, initiate, plan/organize, organization of materials, and task-monitor* scales (Gioia et al.,

2010). Considering the current view of creative processes entailing an iterative interplay between generative and evaluative creative processes, perhaps the capacity to inhibit some ideas in order to focus on others and the broad capacity to self-monitor could be a base advantage to both adaptive behavior and creativity. However, they were not important to creativity in the TD group model.

These results did not show support for the theoretical framework provided by MemiC. For the current study to support this theoretical framework, the creativity model should have been more significant in TD youth since this group would be most similar to typical adults, for whom this framework should fit best. The fact that only the DS model fell in line with the MemiC framework is perplexing, as this indicates support for the framework in atypical youth only. One possible issue may be that the episodic memory task used in the current study (Sea Hero Quest) may not have been a robust enough task to capture the full extent of episodic memory, as it is focused on spatial navigation. Also, this task was a truncated version of the full assessment deemed easier to be completed by participants across a range of ability, and this adjustment may have led to less variance in the typically developing sample. Perhaps including more comprehensive memory measures as well as laboratory-based executive function testing with typical youth and young adults would lead to a better model demonstration of MemiC. It also could be the case that given creativity's quite diffuse neural signature including default mode, executive control and salience networks, a cognitive task-based model is simply not sufficient to explain creativity in typical populations. Further investigation is needed.

An additional question that arose upon reflection deals with the definition of creative products. While the use of the Creativity Assessment Packet (CAP) in the current study provided both verbal and nonverbal tasks, the evaluation criteria for these tasks would seem to fall more under the "novelty" aspect of creativity rather than the "appropriateness" aspect of the construct.

Future studies could also include a participant-driven or researcher-driven evaluation of how "appropriate," "fitting," or "apt" each drawing is to bolster the "aptness" aspect of the data.

Concerning the adaptive behavior scales, surprisingly different group associations were also found. The completely different direction of correlation between creativity and adaptive behavior was unanticipated. It is not clear why creativity would be associated with better adaptive function in the group with DS but with poorer adaptive function in the TD group.

To further investigate the correlations between adaptive behavior and creativity, the Vineland subdomains of socialization, communication and daily living skills were investigated. This process indicated that the creativity-adaptive scales correlations were driven by the communication subdomain of the Vineland. This subdomain was, like the general score, also positively correlated with creativity in the DS group and negatively correlated in the TD group. This suggests that adaptive behaviors and creative processes are likely to be separate processes with unique neural signatures in typical development, but that in the face of impaired communicative skills in the condition of DS, the more communicative ability an individual has, the greater an asset this skill is to the individual's creative performance.

This study had strengths in that novel creativity data for a developmental population were successfully collected and new theoretical work was put to preliminary test. However, this work had limitations in the form of both small participant numbers and its cross-sectional rather than longitudinal design. Additionally, while this study was concerned with products of creativity, it would be interesting to gather both process and product creativity data across the adolescent years in order to better understand how their development occurs. Future studies may find the development of applied creative problem-solving and its behavioral correlates a particularly useful area of study.

Through this study we have explored the development of creative output across the adolescent years in TD youth and youth with DS. In modeling EF and mnemonic contributions to creativity, we provide new information as to creativity's behavioral correlates. We have also included an assessment of how adaptive behavior unfolds across the adolescent years. The directional shifts in the group differences were surprising and merit further examination.

CHAPTER 4

HIPPOCAMPAL SUBFIELDS IN TYPICAL AND ATYPICAL YOUTH: A MANUAL AND AUTOMATED STUDY

Author Note

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Abstract

The hippocampus is a relatively slowly-developing allocortical brain structure in the medial temporal lobe that binds information and assists in its recall. Its postnatal development consists largely of the processes of synaptogenesis, myelination of axons, and synaptic pruning. Down syndrome presents with hippocampal impairment that includes altered prenatal processes as well as alterations in all three postnatal developmental processes. This is the first study to assess the hippocampus and its subfields during its extended development in individuals with DS through the years of adolescence. Group differences between DS and TD participants were expected for anterior hippocampus, CA1 and the combined CA2-4+DG section of the posterior hippocampus as well as the subiculum. It was also hypothesized that CA subfields would correspond to memory, creativity, and adaptive behavior performance. Thirty-eight participants were scanned at 3T and were administered a battery of cognitive tests. Structural T2 and T1 scans were segmented with manual and automated procedures. Manual segmentation yielded group differences for right side CA+DG anterior, CA1 posterior, subiculum, EC, PC, and PHC, and left side EC. Automated segmentation yielded group differences for CA2-3, PC and PHC on the right side and CA2-3, DG and PHC on the left. The two methods showed the highest correlation for CA-DG combined subfields and the lowest for subiculum, PC, and EC. Significant volume-cognitive correlations were found for associative memory and adaptive behavior, and these were both similar between groups. Significant volume-creativity correlations were found only between the subdomain of flexibility and the CA and DG subfields, and only for TD youth.

Introduction

At the time of birth, all major parts of the hippocampus have formed (Arnold and Trojanowski, 1996). However, the processes of axonal growth, synaptogenesis, and myelination continue as the information-processing circuitry both within the hippocampus and between the hippocampus and other brain regions are gradually built and refined over a protracted course of development (Semple et al., 2013).

While it was once thought that the hippocampus was fully developed by around the age of five, recent evidence points to this age as merely adjacent to or around the end of a more rapid rate of the three growth processes mentioned above, rather than a final end to hippocampal development. Specifically, it has more recently been found that brain-wide, the process of synaptogenesis continues into middle adolescence, and that the processes of myelination and synaptic pruning potentially continue even longer (Giedd et al., 1996; Suzuki et al., 2005). Of these three brain-building processes, synaptogenesis and myelination are capable of contributing to volumetric increases, while synaptic pruning could result in slight decreases. One study found that the hilus area of the DG was yet unmyelinated to adult levels at the time of early puberty, (Abraham et al., 2012). There have also been indications that the hippocampus continues to add volume into at least mid-adolescence, with most subfields showing independent trajectories of volumetric increases until around thirteen to fifteen years of age, followed by a levelling off (Krogsrud et al., 2014). Finally, a few studies have found hippocampal volumetric gains into young adulthood (Giedd et al., 1996; Suzuki et al., 2005). If, as Nadel (2022) suggests, it is true that late-developing postnatal neural systems are particularly susceptible to injury and that a postnatal injury may set development on a different trajectory, we see ample evidence in these studies that the hippocampus is one such neural system to be investigated. Figure 1 below

incorporates Figure 2 from Krogsrud et al. (2014) as a visual guide to the non-monotonic subfield volumetric development found in a large study of typically developing children and youth ages four to twenty-two.

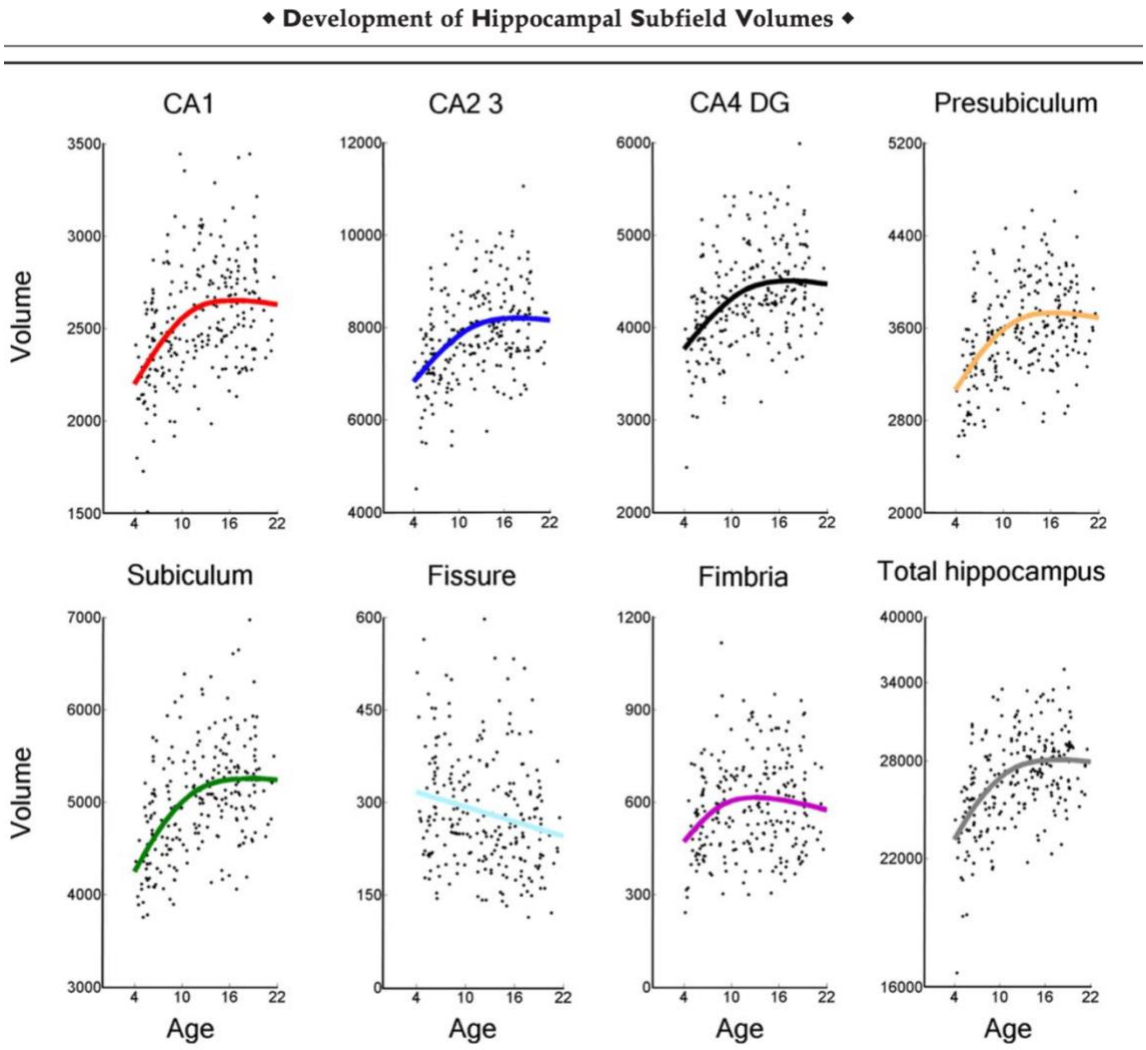

Figure 1. Age-volume plots for hippocampal subfields. From Krogsrud et al., 2014.

Volumetric studies of the hippocampus can be an important starting point to the accumulating body of research linking cognitive functions to specific hippocampal subfields (e.g., Moser and Moser, 1998, Maguire et al., 2000; Poppenk and Moscovitch, 2011; Teicher et al, 2012). This line of research began with important findings about differentiation of the hippocampus along its

longitudinal axis, with the posterior hippocampus specifically associated with spatial processing in rats (Moser and Moser, 1998) and in humans (Maguire et al., 2000). Kjelstrup et al. found place cells also in the ventral hippocampus, suggesting that spatial processing is likely spread out along the longitudinal axis (2008). Subsequent research has shown that the anterior hippocampus is associated with long-term memory encoding (including spatial encoding), while confirming that the posterior is associated with spatial long-term memory (e.g., Fritch et al., 2020).

A separate line of research has focused on assessing hippocampal-cognitive correlations according to histologically differentiated known and named subfields: the dentate gyrus (DG) and cornu ammonis (CA) fields one through four, and peripherally the subiculum and other nearby and highly connected medial temporal lobe gray matter regions. In one developmental study, Lee et al. (2014) found a positive association between posterior right side DG/CA3 volumes and color-item memory in children aged 8-14. Childhood maltreatment has also been studied in relation to subfield volumes and has been found to contribute to volumetric reductions in hippocampal subfields DG as well as CA fields 2-4 (Teicher et al., 2014), suggesting that early stress can impact the range of volumetric development these hippocampal subfields can achieve. There have been a small number of studies of hippocampal volumes specific to development with DS. In one early volumetric study, Pinter et al. found smaller whole hippocampal volumes in young children with DS, indicating that hippocampal size is determined by early developmental differences (2001). More recently, Koenig et al. performed an automated segmentation study of young adults with DS and found smaller volumes bilaterally in CA1, dentate gyrus, and the tail (2021). The CA1 volume was also related to performance on a hippocampally-mediated task (Koenig et al., 2021). In a recent review of previous neuroimaging studies of children and youth aged 0 – 22 with DS, the authors note a persistent increase in medial temporal lobe areas entorhinal and perirhinal cortex as well as volumetric reductions in

parietal and occipital areas (McCann et al., 2021). Finally, a human autopsy study analyzing the brains of children 38 months to three years old with DS produced results consistent with deficits in hippocampal neurogenesis in early postnatal life (Moreno et al., 2021).

These studies add to the research with mouse models that have demonstrated structural abnormalities and impaired short term plasticity at DG-CA3 synapses (Witton et al., 2015) and volumetric differences in the posterior hippocampus as well as the frontal lobes, with fewer neurons found in the DG and CA3, but increased astrocyte and microglia counts as well as increased glutamate (Serrano et al., 2023); the latter suggesting an excitatory/inhibitory imbalance.

This leaves a great many years during the extended, slower period of hippocampal development between middle childhood and young adulthood for which we have no information about subfield development in growing brains of humans with DS. Therefore, the current aim is broadly to fill in knowledge about this topic as a way of preparing for treatment protocols focused on the hippocampus. In the current study, hippocampal subfield volumes are compared via manual and automated estimates for youth with DS and with TD. This is undertaken 1) to gather novel data on subfield development in youth with DS, 2) to compare the gold-standard of manual segmentation to the latest automated segmentation methods in both samples, and 3) to perform a correlational study of hippocampal subfield volumes with the cognitive measures from Chapter 2 of this dissertation. I will first characterize group differences in volumetric development of subfields across the sensitive period of adolescence in youth with DS and TD. Secondly, in comparing automated and manual segmentation I investigate an assumption that the two methodologies are equal and equally valid. While manual segmentation is the gold standard, automated is far more frequently used in research although there is little information as to whether automated methods compare to manual methods for typically developing youth, and no

information that we are aware of for youth with DS. Finally, this study will allow the examination of structural MRI data alongside the cognitive data from Chapter 3 in order to provide data that may help build an understanding of how relevant the hippocampus is to creativity and adaptive behavior. Beyond these immediate aims, this study was also undertaken to determine specific seed regions for the subsequent resting state functional connectivity study.

Specifically, this study is intended to answer the following questions:

RQ1: What differences characterize subfield development in TD and DS youth of the ages 11-21?

H1a: Based on pilot data presented in a 2023 poster, group volumetric differences are expected for the anterior hippocampus, CA1 and CA3/DG of the posterior hippocampus, and subiculum.

H1b: Although this is a cross-sectional study, it is expected that subfield volume development is non-monotonic; statistical modeling may show that nonlinear models fit each group best.

RQ2: Will hippocampal subfield CA volumes correlate with creativity or adaptive behavior in addition to memory in one group or the other?

H2a: Correlation with associative and spatial memory, creativity and adaptive behavior is expected for posterior CA hippocampal sections.

H2b: CA-anterior sections may alternatively correspond better with associative memory.

Methods

Participants

As a subset of the participants described in Chapter 3, 18 youth with DS (M = 15, SD =3.6) and 20 typically developing youth (M = 16.7, SD = 3.2) participated in neuroimaging data collection for this study. Diagnosis of DS was confirmed via physician report of karyotype.

Exclusion criteria included standard MRI counter-indications as well as insufficient ability among the youth with DS to communicate. This was assessed via the ability to verbally assent to the study procedure and a demonstrated ability to follow training instructions and hold the body still while listening to recorded MRI scanner noises during the training session. Two of the initially recruited twenty youth with DS declined to enter the scanner at their sessions and thus participated only in cognitive data collection.

Participants were recruited through local events, via lists of previous participants who agreed to be recontacted, and through state-wide and national posts on DS social media and lists. All aspects of the study were approved by the University of Arizona Institutional Review Board.

As it is generally understood in neuroimaging practice that a sample size of 20 is sufficient for structural imaging studies, a power study was not deemed necessary for this study.

Materials and Procedures

Magnetic resonance imaging (MRI).

Sequences were designed via consultation with imaging specialists with the goal of minimizing time in the scanner. The sequence order was designed to allow for resting state collection first, and then reward participants via the opportunity to watch a video during the structural imaging sequences that followed. The sequences are detailed in Table 1. Structural imaging consisted of T1 and T2 (high resolution) collection in order to capture regional volumes most accurately.

Table 1
Imaging protocol.

Sequence order:			
anat_scout	=	Head Scout	(0:17)
fmap_acq-3mm	=	Field Mapping	(1:50)
func_rest_run-01	=	rsfMRI	(7:00)
anat_T1	=	T1	(5:12)
anat_T2	=	HiRes HPC	(4:22)
Total time:	18:41*		

** The rsfMRI will be repeated after a break if the first run contains too much movement and the participant assents to another try.*

Training for MRI.

Parents in both groups were given training materials created to accustom children to what an MRI scan would be like. The first training material consisted of an MRI storyboard illustrating the imaging center, MRI bed and head cage, and explaining what they would be asked to do in simple words. Additionally, the children were asked to watch at least one of two short videos (~5 minutes) about getting an MRI scan. Parents were instructed to talk to their child about the study and familiarize them with the training materials prior to their study appointment. At the appointment, the researchers asked whether the training materials had been used and reviewed them with the child in all cases. The researchers then listened with the child to a 1-minute recording of some typical MRI sequence sounds with the instruction to sit completely still throughout the duration of the noise. This exercise was repeated one or two times if necessary.

Following training, the child and parent were escorted into the MRI suite, introduced to the technologist, and helped into the scanner. The parent was given the option of staying in the magnet room holding the child's legs, or returning to the control room where they could communicate with the child between each sequence. The imaging session began with resting state and followed with structural image collection. During the resting state scan, participants watched the InScapes video (Vanderwal et al., 2015) with no sound. During structural image collection, participants watched a video of their prior choosing, or continued watching InScapes. Between each sequence, the MRI technologist or the researcher communicated with the

participant to gauge their comfort level and ensure there was no distress. If the child was distressed, the session was paused and the child removed until they were ready to continue. Four youth with DS were asked to participate in repeat sequences due to evident excessive motion. All were willing to do so; two re-entered the scanner on the same visit and two came back the next day. Two youth with TD were also asked to participate in repeat scans and re-entered the scanner on the same visit.

For correlation of subfield volumes with the hippocampal measures collected in this study, we focus on one measure each for associative memory, adaptive behavior, and creativity.

Data Analysis

Pre-processing of magnetic resonance images.

All MR images were initially converted to NIFTI format and processed using the FSL programs deface, fast, and flirt. The decision to use FSL was made before the 2021 publication of Buimer et al.'s study of defacing methods in older adults, younger adults and children. This study implicates FSL deface for removing or blurring some brain data around the ears for children. FSL deface seems nonetheless a reasonable choice for the current study considering that segmentations were accomplished primarily on the T2 images in the current study, which were partial brain images and thus were not defaced. Additionally, Buimer et al. (2021) provide no specific evidence of hippocampal tissue corruption due to defacing. Both manual and automated segmentations secondarily used the defaced whole-brain T1 images. Finally, all MR images were passed through MRIQC for quality control data prior to segmentation and functional connectivity analyses.

Hippocampal segmentation.

Whole hippocampal volume and total tissue volume (TTV) estimates were generated in cubic millimeters (mm^3) via FSL fast. TTV encompasses gray matter, white matter, and CSF. All

whole hippocampal and subfield volumes are corrected by TTV prior to statistical analysis in order to correct for the known phenomenon of smaller TTV in individuals with DS. In order to find the best method for segmenting this special population, hippocampal segmentations were then made both manually and with an automated segmentation program.

Manual segmentation. Manual segmentation into hippocampal subfields was accomplished using ITK-Snap (v. 3.8.0). The current study utilized a protocol described in Ekstrom et al. (2009) and Zeineh et al. (2001) and previously validated in a pediatric sample (Lee et al., 2014). Segmentations used the subfield labels CA anterior (CA1-4 + dentate gyrus subfields in the hippocampal head), CA1 in the body and tail, CA2-4/dentate gyrus in the body and tail, as well as the extra-hippocampal medial temporal lobe regions subiculum, entorhinal cortex (EC), perirhinal cortex (PC), and parahippocampal cortex (PHC) (Ekstrom et al., 2009). Two trained raters (one graduate student and one advanced undergraduate research assistant) manually segmented each hippocampus using the high-resolution T2w images and the T1w images. The two raters' results were compared with a Pearson correlation.

Automated segmentation. Automated segmentation into hippocampal subfields was accomplished using the cloud-based Automated Segmentation of Hippocampal Subfields (ASHS) program with the Princeton Young Adult 3T 1.0 atlas (Yushkevich et al., 2014). Many protocols currently exist, but not all are capable of taking as input both a high-resolution T2-weighted image and a 1.0 mm^3 T1-weighted image as well. Yet it has been demonstrated that 1.0 mm^3 scans alone do not provide sufficient resolution for discriminating one subfield from another (Wisse et al., 2021). Therefore only the automated methods that allowed for two sets of images were considered, and ASHS was chosen from among them as the most highly recommended.

Comparison. A prior study comparing automated and manual segmentation in aging adult samples found a volume discrepancy between the automated and manual segmentations that was larger for clinical samples than for control samples (Sanchez-Benavides et al., 2010). While automated segmentation programs make quick work of what is otherwise a laborious task, they have had mixed reviews as to how well they compare with manual segmentation (e.g., Sanchez-Benavides et al., 2010; Dill et al., 2015; Hurtz et al., 2019).

Results

Whole hippocampal volumes

Whole hippocampal volumes were generated with FSL in preprocessing. As expected, whole hippocampi had reduced volumes bilaterally in the group with DS, confirming results of previous studies (Pinter et al., 2001; Anderson et al., 2013; McCann et al., 2021). Whole hippocampal volumetric group differences are presented in Table 2.

Table 2
Whole hippocampal volumes.

Region	DS mean	SD	TD mean	SD	df	*t*-value	*p*-value	bootstrapped *p*-value
Total Tissue Volume	2.79e6	2.68e5	2.99e6	2.68e5	36	-2.25	0.031	0.034
Right* Hippocampus	10.78	1.94	12.72	1.09	26	-3.75	<.001	<.001***
Left* Hippocampus	9.97	2.38	12.46	0.90	26	-4.19	<.001	<.001***

** Corrected by total tissue volume*

Manual hippocampal subfield segmentation

All 38 brains were successfully segmented according to the manual process indicated earlier (18 DS, 20 TD), although two (both DS) were flagged as lower certainty segmentations due to compromised clarity of images. The two raters' results in mm^3 were compared with a

Pearson correlation. Inter-rater concordance was high (above 94% for most subfields) and is reported in Table 3 below.

Table 3
Inter-Rater Reliability (n=38).

Subfield or Region	DS Sample (*n*=18) Concordance	TD Sample (*n*=20) Concordance
CA/DG-anterior	96.63%	94.80%
CA3/DG (posterior)	98.47%	94.92%
CA1 (posterior)	95.33%	87.00%
Subiculum	96.36%	94.53%
Entorhinal Cortex	96.07%	88.42%
Perirhinal Cortex	98.85%	92.69%
Parahippocampal Cortex	92.73%	84.36%

The two raters' volumes were then averaged to a mean volume, which was used for all subsequent analyses for which the manual segmentations were utilized. Each mean volume was corrected for total brain volume in order to account for overall brain size differences between groups. Subfields were compared between groups using bootstrapped *t*-tests. Based on pilot data presented in an April 2023 poster (Lovos et al., Gatlinburg, 2023), we expected to see volumetric differences between groups in the anterior hippocampus, body CA1, body CA3, and subiculum with reduced volumes in hippocampal subfields and possible increased extra-hippocampal volumes in the group with DS. Final sample results included group differences for the following regions: right side CA/DG anterior, $t(36) = 2.76$, $p = .002$, DS<TD; right side CA1 posterior, $t = 2.19$, $p = .05$, DS<TD; right side subiculum, $t = 2.07$, $p = .046$, DS>TD; right side EC, $t = 2.51$, $p = .016$, DS>TD; left side EC, $t = 2.25$, $p = .03$, DS>TD; right side PC, $t = 3.56$, $p = .002$, DS>TD; and right side PHC, $t = 3.74$, $p < .001$, DS>TD.

Complete results are shared in Table 4.

Table 4

Manual Segmentation of Hippocampal Subfield Volumes, n=38 (n=18 with DS).*

Subfield	DS mean	SD	TD mean	SD	df	*t*-value	*p*-value	bootstrapped *p*-value
CA-anterior - R	3.50	0.64	4.1	0.70	36	-2.76	0.009	0.002**
CA1 (posterior) - R	1.32	0.32	1.51	0.20	28	-2.19	.04*	.05*
CA3/DG (post) - R	1.83	0.56	1.88	0.34	28	-0.33	0.74	0.80
Sub - R	2.83	0.75	2.41	0.45	28	2.07	0.047*	0.046*
EC- R	1.23	0.42	0.94	0.26	28	2.51	0.018*	0.016*
PC- R	0.41	0.15	0.26	0.11	28	3.56	0.001**	0.002**
PHC- R	8.92	2.32	6.79	0.72	28	3.74	.001**	<.001***
CA-anterior - L	3.15	0.74	3.47	0.66	36	-1.41	0.16	0.158
CA1 (post) - L	1.29	0.40	1.48	0.25	28	-1.71	.099	.104
CA3/DG (post) - L	1.74	0.55	1.75	0.28	28	0..024	0.981	0.99
Sub - L	2.52	0.35	2.58	0.67	28	0.29	0.77	0.76
EC- L	1.17	0.42	0.88	0.25	28	2.25	0.031*	0.030*
PC- L	0.41	0.16	0.38	0.28	28	0.67	0.51	0.71
PHC- L	8.14	2.97	6.41	1.51	28	2.23	.035*	.034*

CA = Cornu ammonis, DG = dentate gyrus, Sub = subiculum, EC = entorhinal cortex, PC = perirhinal cortex, PHC = parahippocampal cortex.

** All volumes are averages of the two raters' volumes and are corrected by TTV.*

Automated hippocampal subfield segmentation

Automated segmentation with ASHS made use of both high-resolution oblique hippocampal images as well as 1.0 mm^3 T1-weighted images and yielded 34 segmentations (15 DS, 19 TD); four segmentations failing with this procedure. Two fails were the same participants flagged in the manual procedure that were assessed with MRIQC as lower quality images; two additional brains failed this process for unknown reasons. As with the manual procedure, each mean subfield volume was corrected for TTV.

Significant group differences for measured subfields using the automated procedure were noted for the right side CA2-3 subfield, $t = 2.64$, $p = .004$, DS<TD; and the extrahippocampal medial temporal lobe areas Perirhinal Cortex (PC), $t = 2.12$, $p = .046$, DS>TD; and Parahippocampal Cortex (PHC), $t = 4.04$, $p < .001$, DS>TD. Significant group differences were noted on the left side for the CA2-3 subfield, $t = 2.94$, $p = .006$, DS<TD; and the DG, $t = 3.36$, $p < .001$, DS<TD; as well as the extrahippocampal medial temporal lobe area PHC, $t = 2.45$, $p = .018$, DS>TD.

Complete ASHS results can be found in Table 5 below.

Table 5

Automated Segmentation of Hippocampal Subfield Volumes, n=34 (n=15 with DS).*

Subfield	DS mean	SD	TD mean	SD	df	*t*-value	*p*-value	bootstrapped *p*-value
CA1 - R	2.60	0.47	2.90	0.29	22	-2.15	0.042	0.082
CA2/3 - R	0.82	0.29	1.03	0.13	22	-2.64	0.016	0.004 **
DG - R	2.59	0.54	2.90	0.27	22	-1.97	0.062	0.116
Sub - R	1.22	0.53	1.43	0.2	22	-1.4	0.173	0.12
EC- R	2.22	1.02	2.19	0.35	22	0.14	0.89	0.93
PC- R	10.34	2.25	8.86	0.79	22	2.12	0.042	0.046 *
PHC– R	11.17	2.10	8.86	0.79	22	4.04	<0.001	<0.001 ***
CA1 - L	2.55	0.36	2.63	0.51	22	-0.55	0.58	0.57
CA2/3 - L	0.82	0.29	1.08	0.21	22	-2.94	0.007	0.006 **
DG - L	2.14	0.33	2.47	0.24	22	-3.36	0.003	<0.001 ***
Sub - L	1.70	0.47	1.80	0.27	22	-0.71	0.484	0.474
EC- L	2.22	0.48	1.86	0.34	22	2.47	0.021	0.022 *
PC- L	10.92	2.14	9.37	2.04	22	2.14	0.041	0.08
PHC - L	10.13	2.34	8.52	1.09	22	2.45	0.024	0.018 *

CA = Cornu ammonis, DG = dentate gyrus, Sub = subiculum, EC = entorhinal cortex, PC = perirhinal cortex, PHC = parahippocampal cortex.

** All volumes are corrected by TTV.*

Comparison of manual and automated segmentation

Manual and automated subfield segmentations were compared with Pearson correlations. Four subfields were direct correlates in both procedures: the subiculum, EC, PC, and PHC were directly compared. The automated and manual methods had low to moderate correlation in general (all *rho* roughly .20 - .60), with statistically significant correlations for right side PC for DS ($t = 2.57$, $p = .02$) and for TD ($t = 3.24$, $p = .005$); right side PHC for DS ($t = 2.76$, $p = .01$); and for left side PHC for DS ($t = 2.55$, $p = .02$) and TD ($t = 2.1$, $p = .05$). Hippocampus proper regions were grouped together with other subfields in ways that precluded direct comparison. However, they were instead summed to yield a combined CA1-4 + DG section that could be compared across methods. Correlation coefficients were all moderate or strong for these comparisons (all *rho* roughly .40 - .80) with significant correlations for the right side only (DS right side $t = 2.48$, $p = .03$; TD right side $t = 4.98$, $p < .001$). All comparisons of automated to manual segmentation are shared in Table 6 below.

Table 6
Comparison of Subfield Volumes with Automated versus Manual Segmentation.

Subfield	Manual mean	SD	Auto mean	SD	df	*rho*	*t*-value	*p*-value	Adjusted *p*
Sub ds - R	2.83	0.75	1.22	0.53	13	0.46	1.87	0.08	0.12
Sub td - R	2.41	0.45	1.43	0.2	13	0.19	0.64	0.53	0.55
EC ds - R	1.23	0.42	2.22	1.02	13	0.19	0.74	0.47	0.51
EC td - R	0.94	0.26	3.10	1.48	13	0.26	1.13	0.27	0.34
PC ds - R	4.14	1.52	10.34	2.25	13	0.58	2.57	0.02 *	0.06
PC td - R	4.96	3.93	12.17	6.23	13	0.61	3.24	0.005 **	0.04*
PHC ds - R	8.92	2.32	11.17	2.10	13	0.61	2.76	0.01 *	0.05*
PHC td - R	6.79	0.72	8.86	0.79	13	0.23	0.98	0.34	0.41
CA1-4/DG-ds-R	6.61	0.93	6.01	1.04	13	0.56	2.48	0.03 *	0.08
CA1-4/DG td - R	7.44	0.93	6.82	0.6	13	0.77	4.98	<.001 ***	0.002**
Sub ds - L	2.52	0.35	1.70	0.47	13	0.34	1.28	0.22	0.29
Sub td - L	2.58	0.67	1.80	0.27	13	0.41	1.86	0.08	0.12
EC ds - L	1.17	0.42	2.19	0.48	13	0.03	0.11	0.91	0.91
EC td - L	0.88	0.25	1.86	0.34	13	0.43	2.0	0.06	0.10
PC ds - L	4.09	1.57	10.92	2.14	13	0.23	0.85	0.41	0.47
PC td - L	2.61	0.98	9.37	2.04	13	0.43	1.97	0.06	0.10
PHC ds - L	8.14	2.97	10.13	2.34	13	0.57	2.55	0.02 *	0.06
PHC td - L	6.41	1.51	8.52	1.09	13	0.45	2.10	0.05 *	0.10
CA1-4/DG DS - L	5.5	0.85	6.17	0.83	13	0.50	2.06	0.06	0.10
CA1-4/DG TD - L	6.18	0.74	6.71	0.83	13	0.39	1.76	0.09	0.18

CA = Cornu ammonis, DG = dentate gyrus, Sub = subiculum, EC = entorhinal cortex, PC = perirhinal cortex, PHC = parahippocampal cortex.
** All volumes are corrected by total (brain) tissue volume.*

Subfield volumes across ages

Cross-sectional age-volume plots were created for each subfield and each extra-hippocampal medial temporal lobe area segmented. Manual volumes were used with the exception of the DG subfield, for which only the automated segmentation process captured the subfield in isolation. Volumes were plotted across the ages of 11 to 21 in order to present a snapshot of subfield volumes at each age in this sample. Results suggest non-monotonic development of the hippocampal and extra-hippocampal temporal lobe areas as well as different trends between groups. The participants in the current study represent only the chronologically older half of the range of ages analyzed in Krugsrud et al. (2014) and shown in Figure 1. Therefore the age-volume plots from the current study, found in Figures 2 and 3 below, correspond with the portion of the Krogsrud et al. plots that are more volumetrically stable

between ages 12 and 22. Visual inspection of Figures 2 and 3 indicates greater fluctuation across the ages studied for the group with DS than for the TD group.

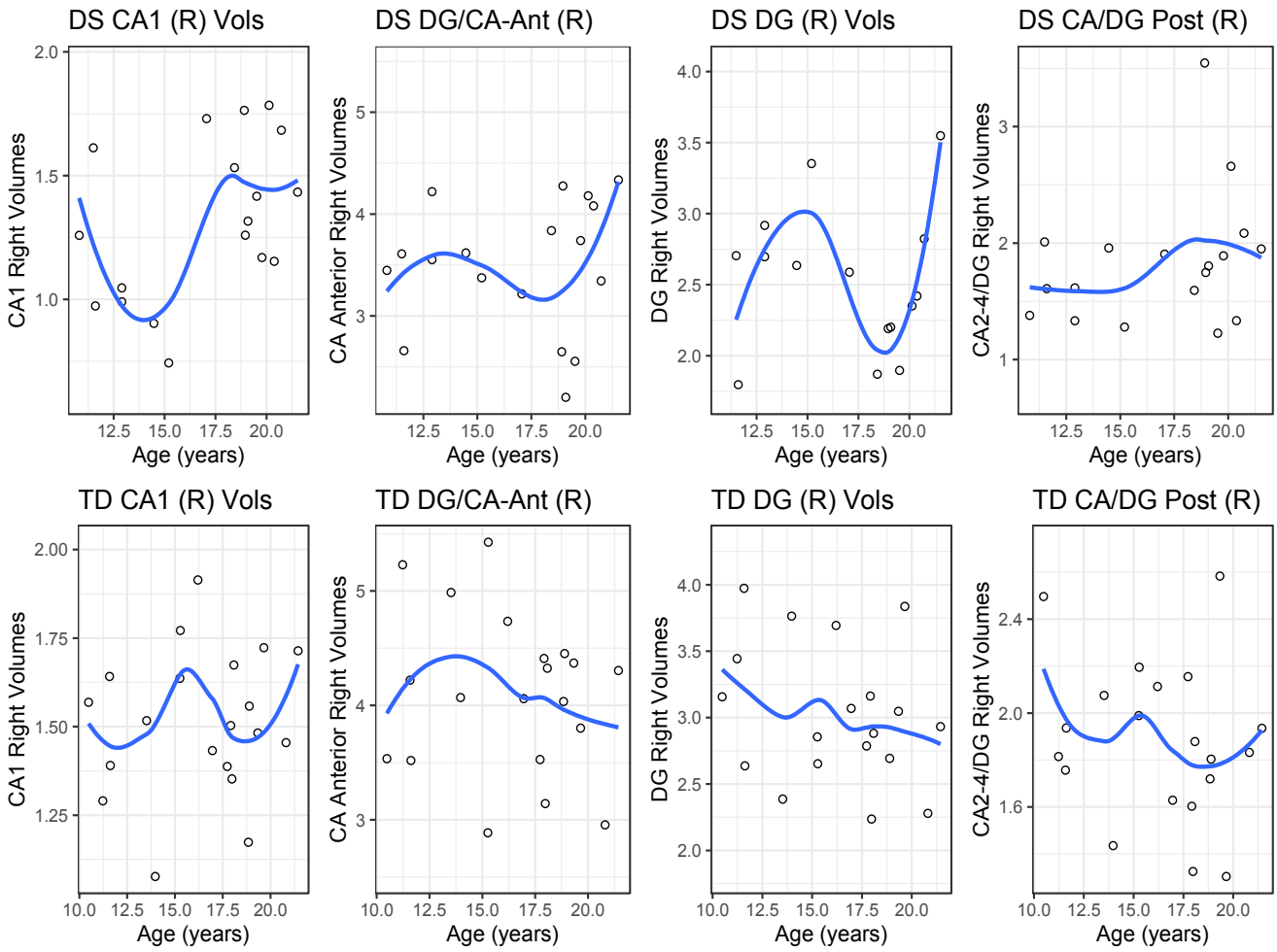

Figure 2. Age-volume plots for hippocampal subfields. Right side volumes are shown.

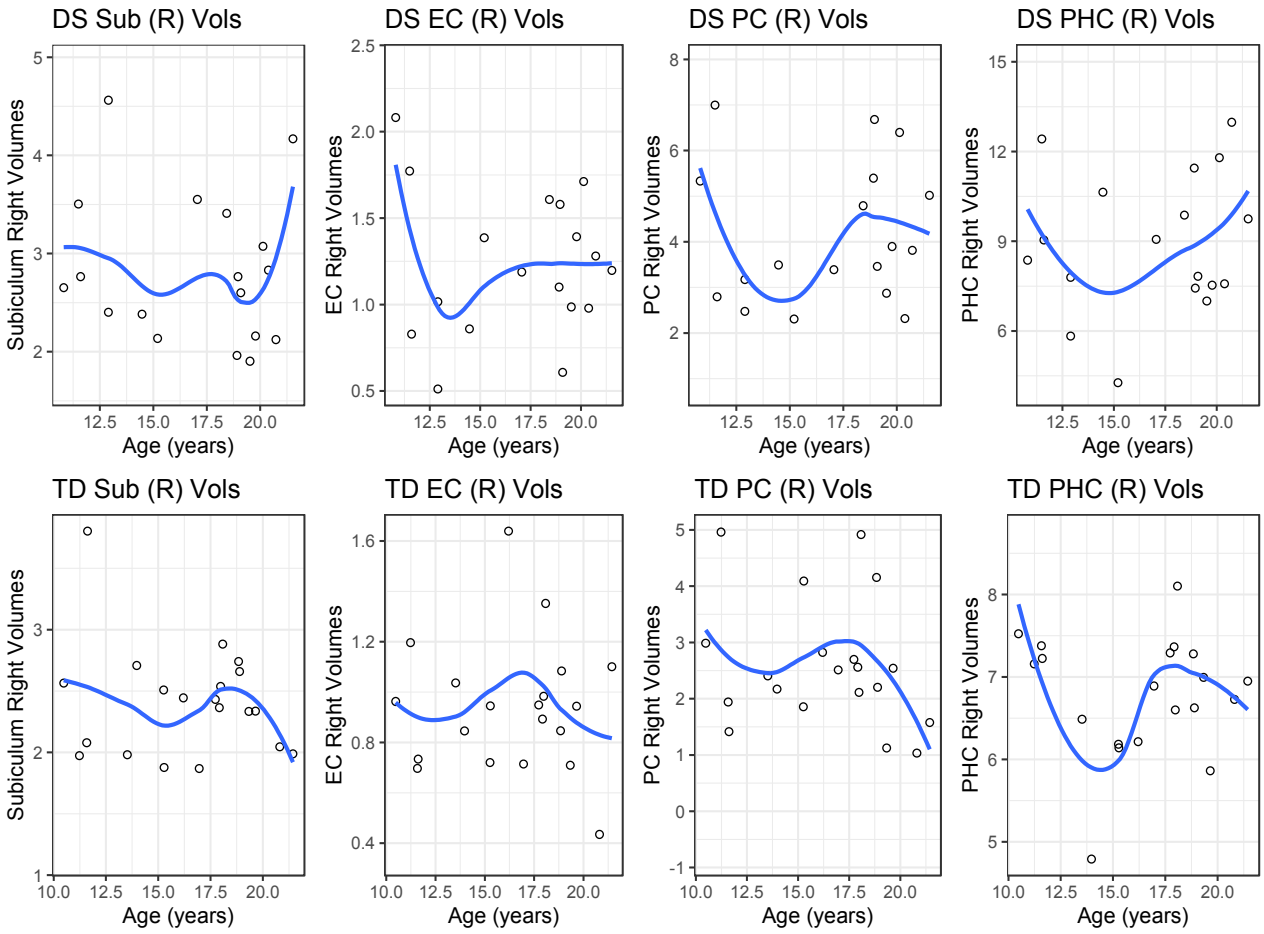

Figure 3. Age-volume plots for extra-hippocampal medial temporal lobe areas. Right side volumes are shown.

Correlations between subfield volumes and neuropsychological tests

CA1, CA2-3, and EC subfields of the right hemisphere were assessed for correlation with the cognitive tests from Chapter 3 of this dissertation. The right side was indicated by previous literature (e.g., Colom et al., 2015; Lee et al., 2014). Data were assessed for normalcy and transformed if needed to correct skewness and kurtosis. Correlations between manually segmented subfield volumes and neuropsychological tests were then assessed via Spearman correlations. These correlational analyses include memory, composite adaptive behavior scores and creativity.

Significant correlations were found for associative memory only with the manually segmented right hemispheric anterior CA+DG combined section. For the group with DS a moderate correlation was found, *rho* = .58, S = 411.1, *p* = .012. For the TD youth, a moderate correlation was also found, *rho* = .55, S = 594, *p* = .011. No significant correlations were found for the indicated subfields with overall creativity, all *p* > .05. For the adaptive behavior composite scores, significant correlations were found for the automated segmentations of the CA1 subfield. A strong correlation was found for the DS group, *rho* = .75, S = 55.25, *p* = .008. For the TD group, a medium-strong correlation was found although it did not remain significant after corrected for multiple comparisons, *rho* = .62, S = 109.69, *p* = .033. Complete results with adjusted *p*-values can be found in Table 7.

Table 7
Cognitive Tests to Manual Segmentation Volumes Correlations.

	Rho	*S*	*p*	Adjusted *p* (fdr)
DS – Assoc. mem. ~ CA+DG Ant., R)	0.58	411.1	0.012	0.05*
TD – Assoc. mem. ~ CA+DG Ant., R)	0.55	594	0.011	0.05*
DS – Creativity (combined) x CA1	0.051	774	0.85	0.99
TD – Creativity (combined) x CA1	0.42	391.8	0.10	0.19
DS – VABS-II x CA1	0.75	55.25	0.008	0.02*
TD – VABS-II x CA1	0.62	109.7	0.033	0.08

Because overall creativity did not correspond to any of the hippocampal subfields, a more detailed correlational study was made of the creativity domains and the hippocampal subfields. In this endeavor a few correlations were noted; the significant associations are described below. Fluency, or the number of drawings produced, was correlated with the automated segmentations for CA2-3 in youth with DS only, *rho* = .52, *t* = 2.2, *p* = .046, although this did not remain significant after correction for multiple comparisons. Flexibility, or ability to shift category of drawing responses, was significantly correlated with manually segmented CA2-4/DG in TD

youth only, *rho* = .55, *t* = 2.56, *p* = .022, adjusted *p* = .05. Flexibility was also positively corelated with manually segmented CA1 subfield for TD youth only, *rho* = .58, *t* = 2.79, *p* = .014, adjusted *p* = .05. There were no significant subfield correlations for the creativity domains of originality or elaboration.

Discussion

Volumes

Based on a previous neuroimaging study of adults with DS using automated segmentation, we expected to see between-groups volumetric differences in subfields CA1 and the dentate gyrus (Koenig et al., 2021). The CA1 (right side) was an area for which the manual method found group differences, but the automated method did not; and the DG (left side) was an area the automated method found group differences for, but that the manual method did not measure in isolation, so this subfield also could not be individually compared. Both manual and automated segmentation found group differences for CA2/3 and the PHC.

The direction of the volumetric differences largely confirmed expectations. As predicted, the DS group generally had larger mean volumes for extra-hippocampal medial temporal lobe areas and smaller volumes for CA and DG areas. This could indicate support for the conclusions of Abraham et al. (2012) in pointing toward decreased postnatal DG neurogenesis in individuals with DS as well as the possibility of delayed or decreased myelination in the hilar region of the dentate gyrus. Since, as Abraham et al. note, septal afferents arriving to the hippocampus are important to synchronizing the hippocampus at a theta frequency during some stages of information processing (encoding during exploration and REM sleep, Buzsaki, 2002), atypical myelination could impair or interfere with the velocity of septal-hippocampal conduction and

thus this could be a mechanism for deficits in hippocampal skills experienced by people with DS (2012).

Age and volumes

Based on prior research into TD hippocampal development across childhood and adolescence (Krogsrud et al., 2014), we expected to find non-linear volumetric development, particularly in the dentate gyrus and CA3 subfields; with potential group differences in timeline and magnitude of change. The age-volume plots of the current study indicate support for these ideas. Age-volume plots for the current study cover the second half of the age range plotted in the Krogsrud et al. study (2014) that was included in Chapter 4 as Figure 1. As can be seen from visual inspection of the current study's age-volume plots in Chapter 4, Figures 2 and 3, older TD youth may have similar or slightly reduced volumes compared to younger TD youth. This suggests the volume-reducing process of synaptic pruning extended across the years of adolescence. The greater variance shown in the DS plots across the different ages may indicate actual greater variance in subfield volumes for DS participants than TD. A similar group difference in variance was shown for the cognitive assessments in Chapter 3: the DS group had a wider range of variance than did the TD group on all measures. This result for volumes could suggest that the brain building processes (synaptogenesis, myelination, and synaptic pruning) may still be more active and not as close to their natural conclusion for this group as they are in the TD group. Alternately, the variation could be due to individual differences. Finallly, it should be noted that some of the variation in these plots may also be based on overfitting due to small sample numbers.

Comparison of manual versus automated segmentation methods

Comparison of the two methods yielded correlations of between .19 - .77. This is generally lower than hoped for. Of note, however, the PC and PHC were significantly correlated

in both groups, and when the CA/DG sections were combined they showed strong and significant correlation on the right side, although not the left. This leaves the subiculum and EC as the most discrepant areas measured.

In most cases, the manual segmentations yielded larger volumes in the hippocampus proper (CA1-4 and DG), while the automated segmentations yielded larger volumes for the extrahippocampal medial temporal lobe regions. One reason for the discrepancies is that guided by what the human eye can see, the manual segmentations were extended further anteriorly than the automated. This could yet be corrected so that segmentations begin and end in the same place along the anterior-posterior axis. Another visible discrepancy is that in some cases, automated segmentations took the medial temporal lobe cortical areas (e.g., the parahippocampal cortex) much further laterally than the manual protocols allowed for, which could account for the larger automated volumes in these areas. However, visual inspection shows that aside from these two issues, most key regions of the segmentations generally correspond to each other in their capture of gray matter regions, although the automated method yields a "spotty" look in some places for which the manual segmentations provide more complete coverage. Visual inspection also suggests that the underlying brain tissue looks more coherent in these, adding support for the strength of the manual segmentations.

In terms of which participant group showed higher concordance between the two methods, the prediction for this study (based on Sanchez-Benavides et al., 2010) was that the TD group would show better concordance. The results of this study confirm this hypothesis, with seven out of ten measured regions for which we could directly calculate correlations showing greater concordance for the TD group. The other three regions, the regions that showed greater concordance for the DS group, were the right side subiculum and the left side PHC and combined CA1-4+DG region. Of note, the automated and manual methods agreed as to which

images were least clear and most difficult to segment. The two that were flagged as lowest certainty in the manual method were failures in the automated method and were also confirmed as the poorest quality with the MRIQC quality evaluation algorithm. Of the other two segmentations that failed on the ASHS platform, one failed due to a missing support file, and one due to unknown reasons.

Altogether the results of this study show some degree of correlation between methods but not enough to dispel the pervasive questions in the field about the validity of automated segmentation programs. It should be noted that the current study used both T1 and high-resolution T2-weighted images in tandem, which offers the automated segmentation algorithm more information that a single image file alone. Therefore the automated segmentation approach adopted in this study should be among the most reliable; many recent studies use only one image file.

Correlation with cognitive assessments

We expected to find that manually segmented anterior or posterior CA subfields correlated with associative memory performance in both groups. The hypothesis favoring the anterior subfields was supported with strong correlations in both groups. This was also found in the Koenig et al. study and was one reason for that study's choice of anterior hippocampal seeds for their subsequent functional connectivity analysis (2021). Based on these results and on the thicker CA and DG slice volumes in the anterior hippocampus leading to greater ease in accurately seeding this region of interest, anterior hippocampal seeds may be indicated for the next step in the current study as well.

We also expected that hippocampal subfield volumes would positively correlate with 1) creative performance and 2) adaptive behavior scores. In the case of creativity data, a few moderate correlations for CA1(manual) and CA2-3 (automated) were noted, but no statistically

significant correlations, all $p > .05$. Deeper examination yielded significant correlations between subfields CA2-4/DG and flexibility and between CA1 and flexibility in TD youth. These findings could offer support for a theory that the domain of flexibility, or ability to shift between different categories of creative drawings, has some overlap with the hippocampal steps of "search" and "construction" from the MemiC framework.

For the adaptive behavior scales, automated segmentation resulted in statistically significant, strong correlations for both groups with the CA1 subfield. A potential reason as to why the manual segmentations did not correlate with adaptive behavior was that the manual segmentations defined CA1 independently only for the posterior hippocampus; for the anterior hippocampus, the CA1 was combined with the CA2,3,4 and DG.

In summary, a few significant correlations were found for hippocampal subfield volumes and hippocampal cognitive functions, but they were different for memory, creativity and adaptive behavior. While greater associative memory corresponded positively to the anterior hippocampus, creativity bore no relationship with subfield volumes, and adaptive behavior corresponded positively with the CA1 subfield in the DS group. An interesting finding was the similar group correlation coefficients for each significant outcome. It was expected that the groups would differ more on the strength of correlation, indicating possible different mechanisms supporting these cognitive functions in the different groups.

GENERAL DISCUSSION

In this dissertation the aim has been to investigate the extended role of the hippocampus across diverse representational functions and across its extended trajectory of development. Diverse hippocampal functions highlighted in these chapters include prediction, exploration, curiosity, statistical learning, and most centrally, creativity and adaptive behavior. These cognitive functions have in common a probable necessity of searching a representational network to support the end goal of each. This relates directly to the constructive episodic simulation hypothesis proposed by Schacter and Addis, which holds that it is episodic memory that enables the flexible assembly and simulation of new mental representations that supports cognitive efforts such as creativity (2007). Assembly of mental representations is fundamentally supported by associative representations and is likely to be guided by the medial temporal lobe and the hippocampus (Schachter & Addis, 2007). In the theoretical article comprising Chapter 2 of this dissertation, we suggest that this important function of the hippocampus needs to be considered in developmental theory in order to understand how the hippocampus contributes to cognitive maturation and how this may underlie changing representational structures (as described by Anette Karmiloff-Smith, 1990). These cognitive functions should now be investigated across development in order to amass a complete picture of the nature and timing of hippocampal contributions to representational capacities.

There is another potential commonality these representational functions may share. The cognitive functions of prediction, exploration, curiosity, creativity and adaptive behavior may share a common mechanism in statistical learning. Statistical learning allows us to make predictions about a present or future phenomenon while minimizing prediction error and thus also minimizing "perceptual uncertainty" (Daikoku et al., 2021). Prediction and curiosity have

already been understood to operate via statistical learning. Prediction is currently understood to be a process continuously utilized by the brain to track both expectations and prediction error, or the difference between predicted and actual data, which is how the brain utilizes previously learned statistical regularities in the environment (Berger & Posner, 2023). PE help us continuously update our implicit statistical knowledge of the likeliness of events or the success of decisions made. The presence of predictive brain activity and PE spikes indicates that statistical learning is occurring, Curiosity, which has been found to enhance memory (Gruber & Fandakova, 2021) can be considered via the lens of the Prediction, Appraisal, Curiosity, and Exploration (PACE) framework (Gruber & Ranganath, 2019). In this model, curiosity is thought to be triggered by prediction errors (PE), PE being the mechanism through which the brain tracks statistical regularities. While this framework is centrally focused on prediction and curiosity, it includes exploration as a means of seeking information in order to assuage curiosity. In this sense, exploration or information-seeking is how one finds out whether a prediction yields the anticipated results and is thus reliant on hippocampal PE (Gruber & Ranganath, 2019).

Adaptive behavior and creativity share some characteristics with prediction and curiosity in that they involve recall of past experiences for use or recombination in the present. This recall certainly includes scenarios relevant to the present and could also involve recall of statistical probabilities surrounding recalled events. A reason this may be a plausible mechanism is that tracking statistical regularities could be quite useful to adaptive behavior and creativity. Statistical regularities, or likelihoods, could help one adapt one's behavior to a given situation through prediction based on past experiences that either play out in reality, or that generate hippocampal PE. A 2015 paper linking statistical learning to adaptive decision-making in a response time paradigm found that participants readily learned environmental statistics and adjusted their cognitive strategies accordingly (Ma & Yu).

In the case of creativity, a 2021 review paper on the statistical properties of musical creativity asserts that there is a growing body of evidence linking creativity in general to statistical learning (Daikoku et al.). Putting this together with the MemiC framework, it is possible that statistical learning could aid in the selection of memories to be recalled for novel recombination in the "search" and "construction" phases of the creative process (Benedek et al., 2023). The novelty aspect of creativity would presumably either operate under a different mechanism or could potentially involve a predictive process in which a larger PE would represent a positive and desired outcome.

Altogether, these cognitive functions are linked in several ways: Neurally, in inclusion of hippocampal input; cognitively, in inclusion of episodic recall; representationally, in that they include abstract cognitive representation and an ability to search one's representational networks; and mechanistically, in the probable involvement of statistical learning. In Chapter Three, I examined some representational cognitive functions for their relationship with memory. I also strove to correlate creative cognition and adaptive skills as related functions with potentially similar neural signatures. In modeling creativity as a function of memory and executive control, a useful model was found only for the group with DS. The strong association of memory and the behavioral regulation index of the executive control assessment contributed to an excellent model fit for the DS group. This index consists of the EF domains of *inhibit* and *self-monitor*, so it could be considered that this finding reflects the interplay of evaluative processes with generative, more memory-based aspects of the creative process as described in the MemiC framework (Benedek et al., 2023).

However, the same model in the TD group explained a negligible amount of the variance in the creativity measure and held no significant correlations. This result is perplexing as memory and executive function, both of which are somewhat impaired in people with DS, were

expected to contribute more to the model in TD individuals and less in individuals with DS. The fact that the opposite was found, with neither memory not executive control substantially contributing to creativity in the TD population, indicates that either the current methodologies were insufficient or that largely different mechanisms support creativity in TD youth. A prime methodology to interrogate could be the parent questionnaires used for executive control and adaptive behavior data, which could have been less accurate for this quite intelligent TD sample with their mean age of 16. In-lab measures for these constructs might be tried in future studies. While questionnaires were chosen for their suitability for and ability to span both groups, they may have less accurately reflected the executive and adaptive behaviors for youth who are typically developing and whose parents may not have been as used to considering their children's behavior in the ways the questionnaires asked of them. As mentioned above, it may also be that that the episodic memory task used in the current study (Sea Hero Quest) may not have been a task close enough to the construct of episodic recall.

If it is the case, however, that largely different mechanisms support creative production in TD youth, perhaps the cognitive tasks used in this study are too specific given the widely dispersed neural signature of creativity that has been found to include complementary activity in the default mode, executive control and salience networks. One plausible partial explanation for the findings could be that semantic memory adds more to creative production than episodic memory in this group. Because the MemiC framework (Benedek et al., 2023) accounts for the inclusion of both semantic and episodic memory, these results are not counter to this theory, perplexing as they may be. This would mean that rather than the episodic simulation hypothesis (Schacter & Addis, 2007), a more semantically based mechanism contributes to the recall and recombination aspect of creativity in the TD population represented by this sample. This is in line with the original associative theory of creativity mentioned earlier (Mednick, 1962) and also

theoretical work by Abraham & Bubic (2015) that points to semantic recall at the root of a number of imaginative faculties including creativity. Yet another possibility could be that the perplexing results for the TD group relate to what Karmiloff-Smith describes as a "representational redescription" (1990). Karmiloff-Smith points to an earlier phase of cognitive development in noting the profound changes between 4-6 year-olds and 8-10 year-olds when asked to create realistic and imaginary items in their drawings. The older group went about creating imaginary items in ways that were more flexible and held greater novelty than the younger group, indicating not only increased cognitive flexibility but potentially, changes in the wiring of the older children's internal representations of real and imaginary items in middle childhood (Karmiloff-Smith, 1990). In the current study, perhaps typically developing adolescence is a separate, later period of representational redescription during which brain networks also undergo change and refinement that are beyond what a cross-sectional study is able to make clear. While the alternative explanations offered thus far for the TD group results have been specific to creativity, they could also be applied to the unanticipated group differences found with adaptive behavior. Creativity held a positive association with adaptive behavior for the DS group but was conversely associated with poorer adaptive function in the TD group. These results fail to support this study's hypothesis, instead indicating potentially different cognitive bases and neural mechanisms for creativity and adaptive behavior in typical adolescent development.

While the CAP drawing and titling task seemed to measure the novelty aspect of creativity well, a question that arose was whether aptness or suitability of the creative output was captured by the task. After finding correlations between the CA subfields and the creativity domain of flexibility in the typical youth, it seems plausible that the domain of flexibility and the MemiC framework "hippocampal" steps of "search" and "construction" could be related.

Although the ability to flexibly shift between categories of drawings would also likely be associated with prefrontal cortex as shifting is an executive control domain, a wider variety of categorical shifts may also relate to richness of recollectable episodes. In Chapter Four, the aim was to characterize group differences in hippocampal subfield development, assess best practices for segmenting youth populations, and correlate subfield volumes with cognitive measures. Group differences in hippocampal subfields and medial temporal lobe areas confirmed expectations and supported previous research. Within the hippocampus proper, the DS group had smaller volumes in all subfields measured, with both methods, in all cases. The DS group also had larger extra-hippocampal medial temporal lobe area volumes by both methods in all cases excepting that of the left side subiculum. This subfield was larger for the TD group according to both methods, and the right hemisphere group differences were more pronounced with both methods. In general, the smaller hippocampal volumes and larger extra-hippocampal regions could be taken as support for the theory that in the face of hippocampal compromise, people with DS may use medial temporal lobe areas in some cases to accomplish tasks that control participants would accomplish using the hippocampus itself (Sakhon et al., 2018).

Although the two methods used for hippocampal segmentation were in absolute agreement as to the direction of every group difference, they were generally correlated only at low to moderate levels with a few stronger correlations arising as exceptions. This implicates the oft-used automated methodology of segmentation as potentially still lagging in validity for segmenting youth, and particularly, youth of a special population. It should be noted that the highest correlation (*rho* = 0.77) between methods was found for the combined right-side CA1-4+DG subfields for TD youth. While this is the only region to be this highly correlated, it is also the most important region, assuming the aim is to assess hippocampal volumes rather than medial temporal lobe regions. This region was followed by the DS parahippocampal cortex (*rho*

= 0.61) and the perirhinal cortex for both groups (TD *rho* = 0.61; DS *rho* = 0.58), all on the right side. Left hemisphere correlations were generally lower, and none survived correction for multiple comparisons.

Age-volume plots indicate greater variance for the DS group than the TD group. This could be due simply to greater individual variation in this group, or could suggest the presence of a longer period of dynamic brain building processes in this group, elongating the developmental trajectory of the hippocampus.

In the final part of Chapter 4 the focus shifted to volume-cognitive correlations. The correlation of anterior hippocampus with associative memory performance in both groups was an anticipated finding. Creativity bore no significant relationship with the hippocampus in this study, which could indicate support for a more semantic basis than episodic basis for creativity. While this still does not refute the MemiC framework, which also includes semantic memory, it does not offer specific support for the idea of the hippocampus (and episodic memory) as foundational to the cognitive representational nature of divergent creative thinking. It is possible, however, that the inclusion of more complete panels of creativity tasks would yield different results. While creativity as a comprehensive metric bore no relationship with hippocampal subfields, finer-grained examination revealed correlations between the creativity domain of flexibility and the CA and DG subfields for TD youth only. I suggest that this correlation could indicate that the metric of creative flexibility may relate to the "search" and "construction" phases of the MemiC framework.

In the case of adaptive behavior, strong and significant correlations were found with the CA1 subfield for both groups. Once again this suggests that creativity and adaptive behavior have distinct neural signatures. These differences between volumetric correlates of associative memory, creativity and adaptive behavior might have gone largely unnoticed if only whole-

hippocampal volumes had been used, indicating the utility of the finer-grained comparisons used in this study.

Strengths, limitations and future directions

This dissertation had strengths in that novel data were collected and analyzed in a developmental population, and new theoretical work was tested. However, this work had limitations in small participant numbers and its cross-sectional rather than longitudinal design. These studies could have benefitted from a wider range of episodic and sematic memory measures, creativity measures including aptness or suitability metrics, and in-lab executive function measures.

A final point regarding Chapter Three has to do with the representational function that is language. In order to communicate our thoughts or provide instructions on a task, we generally must use verbal information. As one group of participants in this study has known language impairments, steps were taken to maximize understanding. Participants were shown the pages of the paper-based task simultaneous to receiving instructions so they could visually see the seed drawings for in the task. An related question for future research may be whether expressive language capacity and creative capacity have a relationship in people with DS, other populations with IDD and typical populations, especially given the correlations found in the current study between adaptive communication and creativity.

Additionally, while this study was concerned with products of creativity, it would be interesting to gather both process and product creativity data across the adolescent years in order to better understand how their development occurs. Future studies may find the development of applied creative problem-solving and its behavioral correlates a particularly practical area of study in both typical and atypically-developing populations. Altogether group differences were more profound than expected, and it is not known whether this is due to stable skill differences

or whether these differences might simply reflect different developmental cognitive stages that either group may yet be moving through. The results of the hippocampal study indicate that development may indeed proceed more slowly for youth with DS than for TD controls, as presaged in earlier theoretical work (e.g., Gomez & Edgin, 2014; Nadel, 2022). The results of the volumetric study indicate moderate comparability between top-quality manual and automated methods currently available to the research community, but also that the automated method should be used with a note of caution, especially with non-standard samples. The cognitive correlations showed that finer-grained hippocampal studies examining subfields rather than whole hippocampi can produce more accurate results, and these can assist in the determination of where connectivity analysis seeds should best be placed.

The three primary parts of this dissertation together present a broader picture of the real-world import of hippocampal development through its involvement in a variety of representational capacities. It is hoped that this theoretical paper and the accompanying two studies underscore the importance of supporting the hippocampus throughout its extended developmental trajectory and of providing rich environmental and learning stimuli for youth throughout this extended developmental timeframe. It is also hoped that this work may add to our growing understanding of the important role the hippocampus plays specifically for the development of persons with intellectual and developmental disabilities, who stand to benefit substantially from treatments that could enhance the performance of the hippocampus.

APPENDIX A:

COGNITIVE DEVELOPMENT IN THE CONTEXT OF HIPPOCAMPAL REPRESENTATION

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Cognitive Development in the Context of Hippocampal Representation

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Abstract

Neuroconstructivist theories of development incorporate an understanding of brain plasticity and connectivity but have yet to fully consider a role for the hippocampus as a connected region helping to shape interactive developmental processes. Accumulating neuroscientific evidence regarding hippocampal representation from the research fields of creativity, curiosity, prediction, exploration, and statistical learning indicates the hippocampus as a dynamic and interactive representational structure that must be considered an important player in development and disorders of development. We discuss the role of the hippocampus in cognitive development and disorders in the context of neuroscientific evidence for hippocampal representation.

Cognitive Development in the Context of Hippocampal Function

Predominant theories of cognitive development emerged in the mid-20th century, prior to the neuroscientific discoveries of the past 40 years. Piaget's theory of cognitive development [1] has been expanded by neo-Piagetian and neuroconstructivist perspectives such as interactive specialization and representational redescription (Box 1; [2-4]; see [5] for a review) to incorporate brain data into our understanding of cognitive transitions. While these new perspectives acknowledged plasticity in brain states and the emergence of cognition from interacting regions, they also prefaced some of our current understanding of the representational capacity of the brain, and specifically how this capacity is driven by hippocampal representation. Here we assert that the accumulated evidence regarding the functions and roles of the hippocampus is both theoretically and practically disruptive for theories of cognitive development. In navigating this disruption, developmental theory must first incorporate the functions of the medial temporal lobe and hippocampus for an accurate characterization of the timing and nature of developmental change.

Based on the concepts of previous developmental theory, we believe the hippocampus may provide some of the mechanism of change in representations first proposed by Annette Karmiloff-Smith in her theory of representational redescription [4]. She posited that mental representations undergo domain-general developmental change in which they gain flexibility. These flexibility gains allow for the integration of generalized and specific details, and this integration may then form the basis for a number of higher level attainments, including creativity [4]. The hippocampus provides an organizational structure that could facilitate the representational development described by Karmiloff-Smith. In Box 2, we summarize the current understanding of the hippocampus' extended development across childhood and adolescence. This extended process must be incorporated into developmental theory in order to build an accurate picture of how the hippocampus may or may not support representation at each stage of development. As noted in neuroconstructivist approaches, development proceeds from the dynamic interaction of neural systems. Here we review new data suggesting that the hippocampus has several coordinating roles, and therefore should be considered in cognitive domains extending beyond memory—including creativity, statistical learning, exploration, prediction, and curiosity. Further, given the nature of hippocampal structure and function, it is sensitive to damage and shows impairments across a number of developmental disorders (Box 3). A number of active clinical trials currently target the function of this region and may need to incorporate new information regarding the hippocampus' role to adequately measure trial outcomes. Understanding the brain's patterns of compensation across disorders is an important avenue to facilitating intervention, and a developmental perspective will be necessary to best understand how the hippocampus' role is present in cognition at various stages and is apparent in behavior. In total, evidence robustly indicates that the hippocampus and associated medial temporal lobe structures must be considered to understand the fundamentals of how cognition develops, is structured, and how we learn.

Developmental Theory Revisited

Piaget contended that cognitive development progresses through stages, first with interactions with the sensory world, and later, with emerging representational schema. Piaget's ideas of late emerging representation have been challenged for decades and form arguably one of the most studied "straw men" in the developmental literature. These challenges have come from infant data [6,7] that suggest early representation across many concepts, with evidence presenting so early in infancy as to suggest to some that representations are innately driven. However, accumulating neuroscientific data from actively navigating rodents and humans [8-10] suggests that space is represented in the hippocampus, and at multiple scales of abstraction [8, 10-11], with coinciding extended developmental trajectories [10]. Grid cells and place cells represent the brain's instantiation of the external world, structuring knowledge and providing pointers to neocortical presentations in a series of conjunctive, hierarchical representations. At the same time, the hippocampus seems to form a relational network that guides broader skills, and subsequently may be related to a number of functional day-to-day outcomes, such as providing the architecture of social relationships, language concepts, and regularities in general [11,12]. In this sense, the hippocampus and its connections provide layers of a developing cognitive structure and are likely part of a hierarchical, domain-general, representational framework supporting higher level cognition. From work on these representations across humans and animals, we know that these attainments continue to develop into the school years and rodent adolescence [10,13, Figure 1]. The bulk of data regarding navigation suggests that while some early representation is present and measurable, it likely differs in its nature from adult-level representation.

While the hippocampus's role in theories of development should be expanded, the hippocampus has already been incorporated into theories of learning for decades. Complementary Learning Systems (CLS) theory suggests that the hippocampus and neocortex have complementary functional properties that the brain can employ, allowing for complex behavior [14,15]. In the hippocampus, we see rapid learning of pattern-separated memory representations; complementarily, the neocortex allows for slower learning of distributed representations [14]. While deep learning models have often used distributed learning approaches that might be termed "neocortical," proponents of CLS theory have proposed that adding a system that would mimic the hippocampal system would help address the prevalent criticisms that such deep learning models are inefficient and lacking in flexibility [14]. Theories rooted in neural structure are thus leading us to better understand how the hippocampus may support a representational system as well as learning mechanisms that complement the roles of cortical structures. Recently the hippocampus has been proposed to support additional "online" cognitive attainments such as creativity, exploration, prediction, curiosity, and statistical learning. The presence of data of this nature encourages us to re-evaluate the role of the hippocampus as a brain structure allowing for representational capacity and predictive cognition in a ways that may drive some of our fundamental higher level cognitive attainments as well as day-to-day behavior.

Beyond Memory

Creativity

Recent studies link creativity to episodic memory and the hippocampus [16-18]. Amnesic patients with episodic memory deficits have also evidenced impairments in divergent thinking tests of creativity [19]. Memory systems likely support creative idea generation by providing a knowledge or experience bank for divergent thinking, which is the ability to generate creative ideas through recombination of a wide array of source information [20]. Creative cognition seems to involve goal-directed memory retrieval—the ability to search both episodic and semantic memory for information relevant to the task at hand [18]. Supporting evidence comes from the recent "episodic specificity induction training" paradigm, which was found to increase memories for episodic detail while not affecting semantic detail generation during a divergent thinking task [21]. When participants were given the episodic specificity induction, they were able to generate significantly more creative ideas than participants who underwent a control induction task. This suggests a position of fundamental importance for episodic memory recall in creative idea generation. Furthermore, creative idea generation could also be essential for generating solutions to problems in diverse real-world contexts [21]. The ability to draw on past experiences to help one arrive at fitting solutions is a day-to-day, adaptive cognitive capacity that adult humans must utilize. What solutions can we imagine if we miss the bus? If we encounter a new problem at work? The involvement of creative ideas and solutions with episodic memory recall supports the representational capacity of the hippocampus as an important element in a connected representational hierarchy.

As creative processes have been shown to draw on memory, so has the cognitive process of imagining future episodic scenarios. Imagining future episodes has been found to draw on the default mode and executive control networks common to episodic memory representation [21-23]. Further evidence that episodic memory is important to the ability to imagine future experiences has also surfaced in studying amnesic patients. Patients who have impaired episodic memory due to hippocampal damage also have trouble imagining their personal futures or new scenarios [24-26]. Notably, there is the example of the amnesic patient DB who could neither remember most of his past nor imagine an episode that might occur in his personal future [27,28]. If we cannot imagine a future, we cannot organize our efforts toward constructing it. This involvement of the hippocampus in representing possible scenarios brings further attention to the hippocampal role in complex cognitive functions that arise as an interplay between various brain regions as brain network connectivity gradually matures. Creativity and future imagining appear to be functions that draw on the later refinement of hippocampal-cortical networks, but we have little data to understand the timing of those developments. We now continue to discuss additional functions which engage hippocampal-cortical dynamics, some of which may be present in infancy and could contribute broadly to cognitive development.

Prediction

Closely linked to future imagining is the faculty of prediction. Predictive coding theories originated to describe the activities of sensory cortices and hold that the brain engages in predictions of the sensory input it will receive. Such predictive processing streams likely represent both predictions and the mismatch between these predictions and original input (prediction error, or PE) [29]. Since we know that remembering time- and context-bound episodes for future recall is central to what the hippocampus does [30], a reasonable question is whether there may be evidence of predictive activity in the

hippocampus as well. Davachi & DuBrow posit that future prediction may be an important aspect of sequencing that helps people plan or act appropriately for an upcoming scenario, and that this may occur specifically via hippocampal sequence learning [31]. This theory is supported by imaging studies that have demonstrated hippocampal sensitivity to repeating sequences (e.g., [32]). Rodent work also establishes a predictive function for the hippocampus. The phenomenon of theta phase precession in hippocampal place cells suggests the presence of predictive coding in the hippocampus related to known locations the animal will encounter ahead in the environment (e.g., 33]). Not only hippocampal place cells, but also the presence of time cells in the hippocampus could support predictive coding in this region (for a review, see [34]). Hippocampal predictive processing may provide evidence for hippocampal involvement in flexible cognition contributing to high-level representations. Fundamentally, it provides evidence of a hippocampal learning mechanism. While there is accumulating interest and work regarding prediction in infancy [35] suggesting that infants are forming prediction errors, thus far data suggests that predictive responses relate to mid-prefrontal Anterior Cingulate Cortex in this early stage. However, connectivity with other regions is not developed until later in childhood. Thus, it seems the human brain is driven to predict, but an open question is how the nature of these predictions change with hippocampal involvement, when that involvement is online, and whether or not there is a functional or learning consequence of that involvement (e.g. representational change).

Exploration

Similarly, the hippocampus is presumed to hold a fundamental role in memory-guided exploration [36,37]. Inherent in memory-guided exploration is an understanding that the exploratory process may involve recall of relevant memories and their comparison with the present moment. This process is thought to involve hippocampal and fronto-parietal network connectivity [36-38] and their interplay. Hippocampal activity in one recent study was associated with successful memory retrieval and predicted subsequent frontoparietal activity more for a retrieval-guided exploration condition than for a control condition in which retrieval did not contribute to exploration [38]. It was also recently demonstrated with hippocampal field potential recordings paired with eye-tracking in presurgical patients that phase-locking at theta peaks preceded fixations to retrieved locations, suggesting that the hippocampus may coordinate memory-directed eye movements in the service of a spatial exploration task [39]. Other work has shown a tight coupling between hippocampal activity and gaze fixations [40]. Such studies indicate that the hippocampus is not only essential to human learning and memory but is also important in guiding what is explored and the depth of the exploration. However, we know very little about the developmental timing for the hippocampus' involvement in exploration in young children. Some studies have suggested that memory-guided eye movements may be in place quite early in infancy [41]. However, those effects have not been examined in conjunction with neuroimaging data, and other behavioral investigations [42] have suggested that those findings must be considered in greater detail, given developmental changes in those effects across age.

Curiosity

Recent studies have also explored the role of the hippocampus in levels of curiosity [43,44]. Because one of curiosity's components is an inherent boost in motivation, it can

be seen as similar to states in which there is motivation toward a reward. Information that reduces uncertainty holds value in state curiosity, just as rewards hold value in a state of reward motivation [43,44]. Largely through its motivational influence, curiosity is proposed to augment learning and memory retention. The Prediction, Appraisal, Curiosity and Exploration (PACE) framework [43] suggests that curiosity is triggered by different events and is instigated through hippocampal prediction errors that are then evaluated or appraised according to our predictions for the future, ultimately leading to further curiosity and explorations toward possible uncertainty-reduction. PACE proposes that this is a curiosity cycle that amplifies memory encoding via increases in attention, exploration, and information-seeking. This augments the storage of information acquired while in a curious frame of mind and is accomplished through dopaminergic neuromodulation of the hippocampus [45]. Recently it has been proposed that the mechanism by which curiosity and surprise affect learning and memory may change over the course of child and adolescent development with enhanced memory resulting from information PEs in adolescents, but not in children [46]. A late-developing ability to learn efficiently from prediction error points to the importance of the slowly developing hippocampus and its late-maturing hippocampal connections with the prefrontal cortex in support of flexible or adaptive behavior, but much more work is needed to understand these links across development.

Statistical Learning

Finally, we consider the cognitive process known as statistical learning, or learning of structure from repeated environmental exposures. This is a process through which we are able to extract regularities necessary for learning about the world, without feedback or reinforcement. Statistical learning is thought to be possible for learners of all ages, although the capacity and mechanism may well change across development [47]. In their review, Forest and colleagues note a developmental trajectory for statistical learning, beginning with fuzzy representations, and advancing to representations that incorporate broad but also specific detail. There are data to suggest hippocampal involvement across all ages [49], although neuroimaging studies have not been consistently conducted.

In an fMRI study with awake human infants, Ellis et al. found that infants as young as 3 months of age demonstrated increased activity in the hippocampus through exposure to statistical regularities [48]. This suggests that infants may be engaged in an early-developing stage of statistical learning, and furthermore, the hippocampus may support statistical learning in infants before it supports episodic memory [48]. This conclusion is consistent with what has been demonstrated in the primate hippocampus regarding the faster development of the monosynaptic pathway (which supports statistical learning) [49] and the relatively slower development of the trisynaptic pathway (linked to episodic memory) [50].

Data from learning disabilities and individuals with intellectual or developmental disorders (IDD) provides some perspective for these data. Individuals with Specific Language Impairment [51] and dyslexia [52] have been noted to show statistical learning impairments, consistent with other data regarding hippocampal involvement. Of interest is that Down syndrome, Williams syndrome, and autism are not accompanied

by deficits in standard statistical learning paradigms [53], a finding that suggests the hippocampus may not be functionally involved in all cases or at all points in development. More work is required to understand when the hippocampus is and isn't involved in statistical learning and other functions such as exploration and predictive errors, and what the functional outcome of that involvement may be. Exploration has been studied in autism and Down syndrome, with both populations demonstrating reductions [54]. Autism has been the most studied to date regarding the broader roles of the hippocampus in outcomes, with conclusions that autistic individuals may have difficulties fully utilizing the hippocampus' hierarchical structure to support social cognition [12].

In summary, creativity, prediction, exploration, curiosity, and statistical learning all have in common the ability to flexibly search a representational network in support of their various goals. The constructive episodic simulation hypothesis [55] posits that the flexible assembly and simulation of new mental representations is enabled by episodic memory, and that this process supports thinking about the future and creative cognitive processes. This constructive process draws on a hierarchically structured representational network, which is conditional in nature and supported by associative representations of various levels originating in the medial temporal lobe and hippocampus. Available data suggest this structuring is accomplished across domains, beyond spatial cognition, and given the breadth of these skills, it is also likely relevant to the accomplishment of day-to-day activities. A process such as this may support a wider array of cognitive skills (i.e., exploration, curiosity and statistical learning) than this hypothesis originally named and must now also be considered in the context of theories of development. It is essential to understand how the hippocampus may contribute and when, as many of these functions are inherent to the cortex itself but may be significantly bootstrapped in some manner when the hippocampus begins to engage in the process (i.e., exploration, statistical learning, prediction). Most data and approaches to hippocampal development would suggest that the hippocampus' involvement in these processes would be extended in time [56], but understanding the trajectory of that involvement and its functional consequences is an important next step for theories of cognitive development (see Figure 1 and Box 2). In Figure 1 we attempt to capture a rough overlap between the studied functions, which from available data all show similarly extended developmental trajectories.

Implications for Developmental Disorders

The research field of intellectual and developmental disorders (IDDs) has often sought core components of cognition that may be related to functional and adaptive outcomes for individuals. Early in autism research, researchers proposed theoretical frameworks such as executive control theory [57] and theory of mind theory [58] as sources of the deficits in day-to-day adaptation in this group. Executive functions have been routinely and consistently examined as a potential core deficit in developmental disorders [59]. Some of these theories have been revisited in recent years with clarifications as to the role of cognitive control functions, qualified as possibly playing a compensatory role when those resources are available [60]. While correlations between executive control, working memory and other outcomes are well-replicated, the primacy of these functions as drivers of future outcomes is not fully established, and other key cognitive mechanisms may be under-recognized. Based on our current thesis, we posit that the hippocampus is involved in aspects of cognitive development and in a number of

developmental disorders via hippocampal-cortical connections. In Box 3, we offer evidence that the hippocampus may be involved across many developmental disorders as a structure sensitive to damage. Hippocampal dysfunction has been observed in IDDs such as Down syndrome, Williams syndrome, Fragile X syndrome, and autism spectrum disorder as well as in learning disabilities such as reading and math disabilities. Box 3 highlights data showing traditional deficits in relation to the hippocampus, such as spatial memory precision and navigation impairments. It is evident from this summary that what is missing is research relating to hippocampal-cortical connectivity and in functions considered to have components of hippocampal involvement beyond episodic memory.

In summary, many of the conditions discussed in Box 3 have been associated with poor prefrontal cortex/executive function, but the role of the hippocampus in broader cognitive and day-to-day skills has been underexplored. Further, findings from these conditions suggest more work is needed to understand why impairments are not uniformly manifested on tasks such as statistical learning, when data suggest hippocampal activity when both infants and adults engage in those tasks. In total, the hippocampus' expanded role is extensive enough, in guiding exploration, prediction and the extraction of regularity, that the field must develop a better understanding of when those roles emerge and how they participate in the structure of cognition under typical and atypical developmental pathways.

Concluding Remarks

Neuroconstructivist theories have addressed the need to understand how brain areas may interact to support emerging cognitive capacities, and in doing so have moved the field forward to discover ways in which neural representations may be molded. Fundamental questions regarding emerging cognition require this perspective, and we also argue the answers will require an understanding of when the hippocampus and memory systems may be involved. For instance, at what point in development does predictive error draw on memory, and how does that manifest in an infant's ability to explore? And beyond, does the involvement of the memory systems and hippocampus modify representation in a qualitatively different way after this structure's functional emergence? The answers to these questions will have major implications for our understanding of the way that the bran represents information, how those representations are modified, and what may be altered when the hippocampus is immature or has altered development.

In some of her final writings, Annette Karmiloff- Smith posited that sleep processes may serve to integrate information across representational networks, allowing for cross-domain use and flexibility [61,62]. We acknowledge the additional hippocampal role during sleep and assert that any theory regarding the hippocampus' support of cognition will have to address how representations emerge and are modified with sleep. Given the hippocampus' role in representation, the processes underway through the brain's emerging specialization could be affected by the influence of the hippocampus. Hippocampal maturity may mark the point at which those specializations are maximized in conjunction with extracted regularities, allowing for flexible use across multiple representational scales.

We began this paper asserting that a new understanding of the role of the hippocampus is theoretically and practically disruptive. Neuroconstructivist theories (notably interactive specialization), which already acknowledge the highly interactive nature of the developing brain, need to elevate the importance of the hippocampus and its connectivity in order to move the theory forward in this field. Incorporating timing of the development of the hippocampus and its connections will be important to this endeavor. This review of the online and predictive cognitive functions reliant on hippocampal function brings the importance of the hippocampus and its connectivity to the forefront. As this sensitive structure and its connections are impaired across a broad spectrum of disorders, targeting its function and connectivity could be important to future cognitive interventions. As a number of active clinical trials currently target hippocampal function, it is important that we understand the full extent and timing of the hippocampus' role in cognitive development and also know how to best measure hippocampus' role in cognition. Are traditional neuropsychological outcomes really sufficient? These recent data suggest that the role of the hippocampus is broader than that, and that what we really want to measure is a proxy for hippocampal-cortical connectivity (i.e., the ways the hippocampus interfaces in broader cognitive functions) and is not limited to long term memory. Further, a developmental perspective will be required, as the functions supported by the hippocampus may undergo significant change as brain networks develop, specialize, and begin to interface with this region. Accumulating data suggest a developmental trajectory of hippocampal function and its integration to support a number of cognitive domains [56]. Given this perspective, it will be important to incorporate an analysis of this structure while studying attainments in vocabulary acquisition [63], academics, motivation, creativity, and even adaptive skills such as work skills.

Figure 1: Modeling the emergence and development of six cognitive functions and the hippocampus

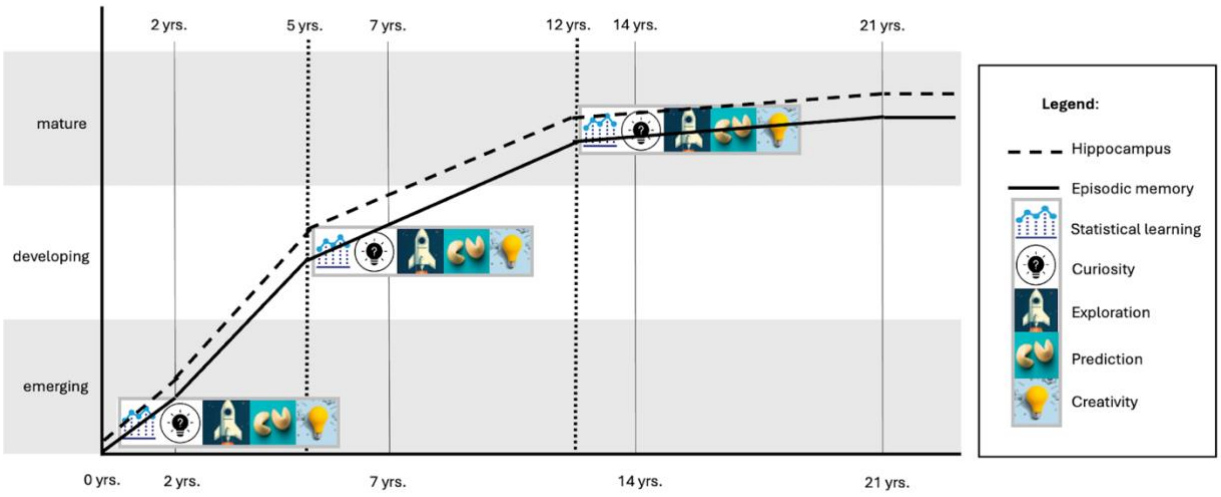

Figure 1. This figure models the development of the hippocampus, episodic memory, and the five cognitive functions explored in this review. More data is required to understand at what point hippocampal (HPC) involvement may support each of them and what effect that role could have on emerging cognitive representations.

HPC: 2 yrs: Tri-synaptic circuit now able to support neural replay during sleep [56]; 4-6 yrs: major shift in HPC memory network connectivity [67]; 7-14 yrs: volumetric increases till at least early adolescence [65]; HPC myelination still underway at 11 yrs old [86]; 14 yrs: ant. and post. HPC connectivity to ventro-medial prefrontal cortex (PFC) increased through mid-adolescence; stabilized in early twenties [66]; age-related increases in connectivity between medial temporal lobe and dorsolateral PFC during memory encoding in teens [87]..
Episodic Memory: 2 yrs: Rapid encoding of contexts of overlapping patterns and retention over sleep delay [56]; 4-6 yrs: context-binding gains [88]; episodic memory gains with memory network strength gains [67]; 7-14 yrs: development of control processes working on memory [88].
Statistical learning: 0-2 yrs: HPC response to statistical regularities as early as 3 months in ant. HPC; presumed to be localized in CA1 and monosynaptic circuit [6]; 7-14 yrs: marked neural differences between learning high vs. low probability events at 12 yrs, coincident with shift to model-based learning [89].
Creativity: 2-4 yrs: Preschoolers are novel in their play [90]; 7-14 yrs: Representational shift in mid-childhood between the ages of 4-6 and 8-10 [4].
Exploration: 2 yrs: Period of high random exploration takes off [91]; 7 yrs: random exploration and levels of uncertainty-directed exploration begin to taper off. Exploring in more sophisticated ways [92]; 14-21 yrs: Highest exploration found around age 18 [93].
Prediction 0-2 yrs: Prediction errors (PE) lead to surprise by 6-7 months old [94]; information PE enhanced memory in teens more than in children [46].
Curiosity: 2 yrs: Scale measures curiosity in children as young as 10 months [95]; 2-7 yrs: curiosity drives learning; associated with better math and reading scores [96]; information PE enhanced memory in teens more than in children [46].

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APPENDIX B:

SEMANTIC DISTANCE

The two verbal creativity measures collected (CAP titles, AMAP noun generativity) were both candidates for semantic similarity analyses; however, both verbal tasks were constrained by low participation numbers, so the semantic analysis from the titles task of the CAP will be analyzed here as it contained a greater number of participants. The semantic similarity measures that were employed were Path Length Similarity (PATH), which sums nodes along the shortest path between the main noun in the titles; and Wu-Palmer Similarity (WUP) to assess the relatedness of depth of a set of titles to assess creative drawing titles on the free platform ws4jdemo.appspot.com.

Methods: The CAP titles had 31 participants (16 with DS). The titles from this assessment were examined through the latent similarity analysis lens of semantic distance measures. Semantic distance is a method of evaluating the similarity between words or phrases in semantic space. At the time these analyses were completed, the most useful free semantic distance platform available was the WS4J Demo (ws4jdemo.appspot.com); it was used to generate the two semantic distance measures PATH and WUP.

Results: Significant group differences were noted for CAP titles $t = 3.29$ ($p<.001$), mean DS group scores 11.6(7.84), mean TD 19.12(5.26). However, there were no significant group differences for PATH or WUP, all $p > 0.05$, mean DS group scores 0.14(0.34) and 0.37(0.46) respectively; mean TD 0.09(0.07) and 0.41(0.12) respectively. Results can be seen in Table 1 below.

Table 1
Descriptive statistics for semantic measures.

	DS			TD			Test		
	n	***M***	***SD***	***n***	***M***	***SD***	***t***	***p***	**Adj. *p***
Titles; CAP	20	11.6	7.84	17	19.12	5.26	-3.29	<0.001***	<o.001***
Titles; WUP	16	0.46	0.37	15	0.41	0.12	0.532	0.81	0.93
Titles; PATH	16	0.14	0.34	15	0.09	0.07	0.543	0.772	0.87

Discussion: No further tests were undertaken due to the small participant numbers for this measure. However, it is interesting to note that semantic distance may be a relatively spared cognitive function for youth with DS, as the groups did not significantly differ on these measures.

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