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Examining the Development of Hippocampal-Dependent Cognition in Young Children: Neuroimaging and Behavioral Approaches

Vanessa Vieites

Department of Psychology, Florida International University, vviei001@fiu.edu

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FLORIDA INTERNATIONAL UNIVERSITY

Miami, Florida

EXAMINING THE DEVELOPMENT OF HIPPOCAMPAL-DEPENDENT
COGNITION IN YOUNG CHILDREN: NEUROIMAGING AND BEHAVIORAL
APPROACHES

A dissertation submitted in partial fulfillment of

the requirements for the degree of

DOCTOR OF PHILOSOPHY

in

PSYCHOLOGY

by

Vanessa Vieites

2021

To: Dean Michael R. Heithaus
College of Arts, Sciences, and Education

This dissertation, written by Vanessa Vieites, and entitled Examining the Development of Hippocampal-Dependent Cognition in Young Children: Neuroimaging and Behavioral Approaches, having been approved in respect to style and intellectual content, is referred to you for judgment.

We have read this dissertation and recommend that it be approved.

Anthony S. Dick

Aaron Mattfeld

Benjamin Baez

Shannon M. Pruden, Major Professor

Date of Defense: March 23, 2021

The dissertation of Vanessa Vieites is approved.

Dean Michael R. Heithaus
College of Arts, Sciences, and Education

Andrés G. Gil
Vice President for Research and Economic Development
and Dean of the University Graduate School

Florida International University, 2021

DEDICATION

For Bethany, whose wisdom and mentorship inspired this project.

For Mami and Papi, who supported me throughout this journey.

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This dissertation would not have been possible without the support of several people in my life. Throughout the last seven years, many tears were shed, mistakes made, and lessons learned, so as this era comes to an end, I would like to give many thanks to those who made sure I kept calm and carried on.

First and foremost, thank you to my late advisor, Dr. Bethany Reeb-Sutherland, whose light and laugh I will always remember, for taking me on as one of her first graduate students, helping me hone my research and writing skills, and always pushing me to do more than I thought I was capable of. May she rest in peace. Secondly, thank you to my current advisor and long-time collaborator, Dr. Shannon Pruden, for introducing me to the world of spatial research, always maintaining a positive attitude, and believing in me even when I doubted myself. Additionally, I would like to thank others in my academic circle—at FIU and elsewhere—for their constructive feedback on this and other related projects: Drs. Anthony Dick, Aaron Mattfeld, Timothy Hayes, Stefany Coxe, Anna Shusterman, and Nora Newcombe.

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ABSTRACT OF THE DISSERTATION
EXAMINING THE DEVELOPMENT OF HIPPOCAMPAL-DEPENDENT
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by

Vanessa Vieites

Florida International University, 2021

Miami, Florida

Professor Shannon M. Pruden, Major Professor

The current dissertation examined neurological and behavioral approaches to studying the development of large-scale spatial cognition and its underlying neurobiology in young children. Study one reviewed the literature on the development of the neurobiology of spatial navigation and reorientation, including the hippocampus and the parahippocampal, parietal, and prefrontal cortices, and discussed how researchers can overcome the challenges of studying these brain-behavior relations in young children. One solution, I propose, is to employ a hippocampal-dependent form of associative learning known as Pavlovian Trace Eyeblink Conditioning (EBC) to assess hippocampal functioning indirectly and safely in pediatric populations. For the following two empirical studies, children between the ages of four and six years completed three structural magnetic resonance imaging scans (MRI), a hippocampal-dependent eyeblink conditioning paradigm, a spatial reorientation test, a left-right assessment, the Boehm-3 Preschool Test of Basic Concepts, and two control tasks, the Children's Mental Transformation Task (CMTT) and the NIH Toolbox Pattern Comparison Processing

Speed (PCPS) Test. Study two (N=31) examined the validity of using a child-friendly, hippocampal-dependent measure of associative learning (i.e., trace EBC) as a proxy for hippocampal function and efficiency. Results revealed that individual differences in greater neurite density of the bilateral hippocampus, but not the cerebellum, predicted later, and thus more efficient, timing of learned associations between auditory and tactile stimuli. Study three (N=39) investigated the role of spatial language on children's spatial reorientation strategies and outcomes. Findings showed that, independent of age, children who could comprehend relative locations such as left and right, as opposed to general relational concepts, were better at encoding the geometry of a room to recall the location of a hidden object after being disoriented. Implications, limitations, and suggestions for future studies with young children are discussed.

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LIST OF ACRONYMS AND ABBREVIATIONS

Cerebellum	Cer
Children's Mental Transformation	CMT
Children's Mental Transformation Task	CMTT
Conditioned Response	CR
Conditioned Stimulus	CS
Correct	C
Dentate Gyrus	DG
Developmental Systems Theory	DST
Diagonal	D
Diffusion-Weighted Imaging	DWI
Electroencephalography	EEG
Eyeblink Conditioning	EBC
Far	F
Functional Magnetic Resonance	fMRI
Head Direction	HD
Hippocampus	Hipp
Interstimulus Response	IR
Intraneurite Volume Fraction	INVF
Left	L
Magnetic Resonance Imaging	MRI
Maximum	Max

Mean	M
Microstructure Diffusion Toolkit	MDT
Milliseconds	ms
Minimum	Min
Near	N
Neurite Density Index	NDI
Neurite Orientation & Density Diffusion Imaging	NODDI
Number of participants in sample	N
Pattern Comparison Processing Speed	PCPS
Pounds per square inch	Lb/in ²
Region-of-Interest	ROI
Right	R
Socioeconomic Status	SES
Standard Deviation	SD
T1-8	Trial 1-8
Two-dimensional	2D
Unconditioned Response	UR
Unconditioned Stimulus	US
Williams Syndrome	WS

STUDY I: WHERE DO WE GO FROM HERE: REVIEW OF THE NEUROBIOLOGY
AND DEVELOPMENT OF SPATIAL NAVIGATION AND REORIENTATION IN
CHILDHOOD AND BEYOND

ABSTRACT

Remembering where you left your keys, finding your car in a crowded parking lot, locating items on a map, and navigating through an unfamiliar neighborhood are all tasks that require spatial skills, such as spatial memory, navigation, and reorientation. These spatial skills are adaptive functions that are critical for survival. The hippocampus, a structure located within the medial temporal lobe of the brain, plays a vital role in the formation of spatial memories, continuing to develop after birth and, in some cases, exhibiting experience-dependent plasticity. Furthermore, an intricate system of brain regions, including the parahippocampal, parietal, and prefrontal cortices, also contributes to successful spatial navigation and reorientation. Although much is understood about the development of spatial memory abilities in adults and non-human animals, relatively little is known about the development of the hippocampus in relation to these malleable skills in early childhood. In part, this is because common techniques such as Functional Magnetic Resonance Imaging (*fMRI*) used to examine underlying brain activity in older children and adults are difficult to obtain in young children, complicating the study of brain development. In this chapter, I discuss the development and measurement of the neurobiology of spatial navigation and reorientation abilities and how researchers may overcome the challenges of studying these brain-behavior relations in young children.

Keywords: neurobiology of spatial memory, development of spatial memory, hippocampus, spatial navigation, reorientation, neuroimaging, eyeblink conditioning

LITERATURE REVIEW

Introduction

Anyone who has ever found themselves lost while driving in an unfamiliar neighborhood or has forgotten where they parked their car can appreciate the importance of being able to navigate their environment. Understanding three-dimensional space and the relations between objects and features within it, broadly known as spatial cognition, is an essential part of human intellect—one that encompasses different cognitive and behavioral domains with distinct underlying neural systems. One such domain is spatial navigation, which relies on the medial temporal lobe structure known as the hippocampus, particularly the right side in humans (Burgess, Maguire, & Keefe, 2002). The hippocampus continues to develop after birth (Gogtay, Nugent, Herman, Ordonez, Greenstein, Hayashi, ... & Thompson, 2006) and may exhibit structural changes caused by wayfinding (i.e., navigation) experiences (Maguire, Gadian, Johnsrude, Good, Ashburner, Frackowiak, & Frith, 2000). However, the hippocampus is not the sole contributor to spatial navigation. For instance, a network of brain regions, including the parietal and retrosplenial (Clark, Simmons, Berkowitz, & Wilber, 2018) cortices, also play an important role in aspects of this large-scale spatial ability.

Although much is understood about the underlying neurobiology of spatial memory in adults and non-human animals, relatively little is known about the development of the hippocampus in relation to these malleable skills in children. For one, popular techniques used to examine underlying brain activity in non-pediatric populations are not always suitable for examining hippocampal development in young children. Thus, it is crucial to explore novel yet viable ways to collect such sensitive data in young

children. Coming from a developmental systems perspective, in study one, I provide an overview of the development of large-scale spatial cognition and its underlying neurobiology as well as the typical methods used to measure the neural correlates of spatial abilities. Moreover, I discuss promising new avenues for optimizing the study of hippocampal-spatial relations in young children.

Looking at Spatial Cognition Through A Developmental Systems Lens

Developmental systems theory (DST) stresses that human development is complex, dynamic, and influenced by many co-acting forces, and highlights the importance of considering both inter- and intra-individual differences in developmental trajectories and outcomes. As such, spatial memory abilities are neither fixed nor the result of one determinant (e.g., brain development). Instead, the development of spatial skills is influenced by a series of factors interacting to affect how and when they emerge. By examining a multitude of factors that may be related to the development of spatial abilities, spatial memory researchers can comprehend not only typical trajectories in spatial cognition but also how social and biological factors intersect to create individual and group differences in developmental outcomes.

The field of developmental psychology was once comprised of domain and context specific “minitheories,” or, more adequately, hypotheses, that addressed the development of specific behaviors (i.e., motor development, attachment) within specific contexts (Witherington, 2007). In the early 90s, however, research scientist Esther Thelen conceptualized a unifying, all-encompassing theory of development (Thelen, 1992). Thus, dynamic systems theory arose as a holistic, relational, and integrative account of development (Fischer and Bidell, 1998)—one that would transcend the feud between

nature and nurture as causal explanations of behavior that was historically prevalent in developmental science (Lerner, 2006). From a dynamic systems perspective, change in developmental systems is non-linear (Witherington, 2007). Proponents of dynamic systems theory are interested in how global order (development) emerges from local variability (individual differences in behavior).

One dynamic systems approach to the study of development, endorsed by Thelen (1992), then Thelen and Smith (1994, 1996, 2003), and later Spencer and colleagues (2006), focuses on how specific actions occurring within a context in real time explain the emergence of behaviors. For example, Thelen and colleagues conceptualized the concept of embodied cognition—that *knowing* is equivalent to moving, perceiving, acting, and remembering occurring together within an environmental context in real time. Smith and Thelen (2003) described two major concepts of their dynamic systems approach. One is that behavior is multi-causal. In other words, as opposed to being hard-wired, behavior is determined by multiple parts of the system—from the molecular to the cultural—that softly assemble to create the whole of development. Thus, no part of the system takes causal priority in driving development because all parts are necessary. The second major concept of Smith and Thelen's (2003) dynamic systems approach is that behavior is nested in real-time. Developmental time, then, is the accumulation of events happening within contexts in real time.

In accordance with a dynamic view of development, it is evident that people do not move through the world as passive recipients of their environments. They explore, interact with, and often change their surroundings (Ishikawana, 2020). The concept of human-environment interactions and their influence on spatial development can be

grounded in J. J. and Eleanor Gibson's ecological theory of perception (Gibson, 1979; Gibson & Pick, 2000), in which they developed the idea of affordances—opportunities the environment offers for organisms to be active. Echoing a developmental systems perspective, the ecological approach to development says that organisms cannot be teased apart from their physical environments because the two “make an inseparable pair” (Gibson, 1979). According to the Gibsons, perceptual development involves increasing the efficiency of perception because of experiences. They asked, what does the environment do for, or afford, us and what can we learn from it? Beginning in infancy, for example, humans perceive what they can and cannot do within their environments through exploratory locomotion, both self-directed and accidental. They thus extract information from stimulation, learning which environmental properties are constant and which are changing (Ishikawa, 2020), taking advantage of their affordances (e.g., environmental layouts that allow for movement), and receiving consequences for their actions in the form of successes and failures.

Motor development drives much of the ability and motivation children have to explore their environments, making it an important, though not sole, prerequisite for spatial cognitive development (Mulder, Oudgenoeg-Paz, Hellendoorn, & Jongmans, 2017). In keeping with a dynamic systems perspective, spatial skills emerge because of the interactions between a child and their environment, interactions that change over time as children learn to navigate the space around them independently. As infants learn to sit, crawl, walk, and eventually run, they encounter additional attributes of the spatial world, discovering the relations between themselves, others, and objects, as well as figuring out distances and depths (Mulder et al., 2017). In doing so, they are constantly learning what

the environment can afford them—that is, new opportunities for spatial activities, which promote further development of spatial cognition.

The Spatial Brain: On Navigation and Reorientation

Spatial memory allows us to mentally represent our three-dimensional surroundings and the positions of objects relative to other environmental features. Spatial reorientation, more specifically, refers to the ability to re-establish a sense of direction when navigating. Without spatial navigation and reorientation skills, everyday tasks such as remembering where you left your keys, finding your car in a crowded parking lot, and navigating through unfamiliar neighborhoods would be made virtually impossible. The hippocampus of humans and other animals has long been implicated in spatial navigation (Wills, Muessig, & Cacucci, 2014) and, more recently, in virtual reorientation in human adults (Sutton & Newcombe, 2014). Four decades ago, O’Keefe and Nadel (1978) proposed the theory that the hippocampus forms a cognitive map of the environment, representing locations and their contents, which permits humans and other animals to encode spatial relations and traverse their surroundings using allocentric and egocentric frames of reference.

Allocentric and egocentric wayfinding strategies are utilized in learning locations in the environment, known as place learning (Waller, Loomis, Golledge, & Beall, 2000). Allocentric strategies involve encoding the relations between objects and/or landmarks, while egocentric wayfinding strategies include encoding the body’s position and movements in relation to other objects in the environment. Research shows that the hippocampus is critically involved in the use of allocentric spatial strategies (i.e., mapping the relations among multiple, fixed landmarks in the environment to navigate;

Astur, Taylor, Mamelak, Philpott, Sutherland, 2002), such that individuals with hippocampal resections show impaired performance on a task that requires them to locate an object on a virtual 8-arm radial maze with landmarks at a distance (Bohbot, Iaria, & Petrides, 2004).

The ability to navigate and reorient in space requires that one can know where they are in the environment (i.e., place learning) and where they are headed (e.g., directionality), respectively. In rats, understanding location, or ones “place field,” relies on place cells in the hippocampus (Burgess & O’Keefe, 1996; O’Keefe & Burgess, 1996; O’Keefe & Conway, 1978; O’Keefe & Dostrovsky, 1971), whereas calculating directionality, regardless of location, depends on head direction (HD) cells located in the hippocampus (i.e, postsubiculum; Taube, Muller and Ranck,1990) and anterodorsal thalamus (Zugaro, Berthoz, & Wiener, 2001; Muir & Taube, 2002). The place cell system and HD cell system function similarly, with both types of cells firing with respect to background (e.g., distal), rather than foreground (e.g., proximal), cues in the environment (Cressant, Muller, & Poucet, 1997; Zugaro et al., 2001). Furthermore, HD cells have also been found in other brain regions in rats such as the lateral dorsal nucleus of the thalamus (Mizumori & Williams, 1993), the lateral mammillary nuclei (Stackman & Taube, 1998), the retrosplenial cortex (Chen, Lin, Green, Barnes, & McNaughton, 1994), and the dorsal striatum (Wiener, 1993) (for a review of HD cell firing properties, see Taube, 1998). Furthermore, animals that engage in behaviors that require them to remember spatial locations, such as food-storing Chickadees, have larger hippocampi than animals that do not engage in such spatial behavior (Hoshooley & Sherry, 2007).

Studies with humans implicate the hippocampus, parahippocampus, and parietal cortex as critical brain regions that facilitate spatial navigation abilities. Specifically, in a virtual navigation study of single-unit cell recordings, cells that encoded locations (i.e., place cells) were found mainly in the hippocampus, whereas cells that responded to views or scenes of landmarks were found mainly in the parahippocampal region (Ekstrom, Kahana, Caplan, Fields, Isham, Newman, & Fried, 2003). Furthermore, data supports interactions between the hippocampus and the parietal cortex during learning, consolidation, and retrieval of spatial information. For instance, some studies find that spatial information is initially processed in both the hippocampus and parietal cortex, but later transferred from the hippocampus to the parietal cortex for long-term storage (Kesner, 2000). Hence, a network of brain regions appears to support spatial navigation and reorientation abilities, at least in adults.

The underlying neural processes that facilitate, specifically, spatial reorientation implicate the hippocampus and striatum (for a review see, Sutton & Newcombe, 2014). Evidence from *fMRI* studies supports the hypothesis that the hippocampus encodes geometric information, while the striatum encodes landmark information (Doeller & Burgess, 2008; Doeller, King, & Burgess, 2008). These studies demonstrate that learning where an object belongs relative to a boundary activates the hippocampus, while learning where an object belongs in relation to a landmark activates the dorsal striatum. However, reorienting by a feature (i.e., colored wall) along a boundary (i.e., rectangular enclosure) also activates hippocampal place cells, while reorienting by features within an enclosure does not (Cressant et al., 1997). Moreover, in virtual reorientation studies with adults, significantly greater hippocampal activation following disorientation was found in

conditions where a feature was present (Sutton, Joanisse, & Newcombe, 2010; Sutton, Twyman, Joanisse, & Newcombe, 2012). These results highlight the specific importance of the hippocampus in combining geometric and landmark cues for reorienting.

Therefore, if the hippocampus is recruited during spatial reorientation tests involving both geometric and landmark information, then a less mature hippocampus would contribute to lower performance in combining these strategies for reorienting.

The Developing Spatial Brain

Data on biological and experiential factors underlying the development of spatial abilities have sparked a chicken and egg debate: does normal brain maturation lead to improvements in spatial cognition or does the practice of spatial activities, like navigating, stimulate hippocampal development? The answer is complicated by the fact that while infants are not born into the world as “blank slates,” they certainly come into an inherently spatial world—one that is three dimensional and full of different shapes, sizes, and depths. Hence, both biological and experiential factors drive age-related changes in spatial skills, but brain (e.g., hippocampal) maturation and spatial competence likely influence one another (Vasilyeva & Lourenco, 2012).

If the hippocampus plays a crucial role in large-scale spatial cognition, then it stands to reason that the development of this critical brain region would contribute to children’s emerging abilities to encode spatial relations (for a review see Vasilyeva & Lourenco, 2012). However, most neuroimaging studies related to spatial navigation and reorientation have been conducted with adults, but recent research by Murias and colleagues (2019) suggests that that preadolescent children may not engage their hippocampus as much as adults do while reorienting. Specifically, the authors found that,

compared to young adults, 10-12-year-old children performed worse on a virtual reorientation task while in the scanner, having increased neural activity in non-hippocampal areas of the brain associated with visuospatial processing and navigation (i.e., left cuneus and mid occipital area, left inferior parietal region and precuneus, right inferior parietal cortex, right precentral gyrus, cerebellar vermis and bilateral medial cerebellar lobes; Murias, Slone, Tariq, & Iaria, 2019). Furthermore, functional connectivity analyses showed that adults had increased connectivity from the right hippocampal/parahippocampal gyrus to the contra lateral caudate, the insular cortex, and the posterior supramarginal gyrus, while children had increased connectivity from the right paracentral lobule to the right superior frontal gyrus (Murias et al., 2019).

Furthermore, to study hippocampal-dependent learning and spatial memory in young children, an age group in which functional magnetic resonance imaging (fMRI) is normally not feasibly obtained, Vieites and colleagues (2020) found a positive relation between hippocampal-dependent eyeblink-conditioning, a form of associative learning, and reorienting by geometric cues on a spatial reorientation test in 3-6-year-old children.

For one, the hippocampus of humans and non-human animals is not fully formed at birth, and, thus, brain immaturity is reflected in early deficiencies in hippocampal-dependent behaviors, such as spatial navigation in mobile species and episodic memory in humans. For instance, evidence shows that the rat hippocampus reaches maturity between the 4th (Altman & Das, 1965) and 7th (Pokorny & Yamamoto, 1981) week after birth, while hippocampal synaptic connectivity matures at 5 years of age (Seress, 2001). Furthermore, normal human hippocampal development can continue into early adulthood (Gogtay, Nugent III, Herman, Ordonez, Greenstein, Hayashi, ... & Thompson, 2006).

Thus, it is reasonable to suggest that significant age differences in performance on hippocampal-dependent spatial tasks reflect different developmental stages of the hippocampus. For example, Chapillon and colleagues (1995) found that, compared to 5- and 9-week-old mice, 3-week-old mice had significantly more trouble locating food by orienting to distal cues on an 8-arm radial maze. Similarly, children under the age of 3.5 years have difficulty forming allocentric relations among cues to locate rewards (Ribordy, Jabès, Banta-Lavenex, & Lavenex, 2013), as well as reorienting by features along a geometric boundary (Vieites, Pruden, Shusterman, & Reeb-Sutherland, 2020). These findings coincide with research on memory in young children, in which children under the age of 2 years are unable to form episodic memories (Bauer, 2014). In contrast, children between the ages of 4 and 6 years improve dramatically in their abilities to recall the details of events (Bauer, Pathman, Inman, Campanella, & Hamann, 2017; Drummey & Newcombe, 2002). Thus, it appears that the hippocampus undergoes a pivotal shift in development between 4 and 6 years of age—the very same period in which children begin to exhibit success on a variety of hippocampal-dependent tasks, including spatial reorientation tasks (Learmonth, Newcombe, Sheridan, & Jones, 2008).

With regard to atypical development, individuals diagnosed with Williams Syndrome (WS), a genetic defect that impairs hippocampal development and visual-spatial abilities (Bernardino, Mouga, Castelo-Branco, & van Asselen, 2013), have difficulty using the geometric properties (i.e., shape) of a relatively small enclosure (~6' x 4') to locate a hidden object, compared to controls (Lakusta, Dessalegn, & Landau, 2010). However, these individuals can use a distinct feature (i.e., colored wall) as a cue to the goal location. Thus, these findings suggest that the hippocampus is particularly

involved in the geometric processing of spaces. Given that the hippocampus undergoes significant development during the first 5 years of life, then an immature hippocampus would possibly hinder a young child's ability to reorient by using certain features, such as geometric information or a combination of geometry and landmarks, in the environment.

On the other hand, other research shows that spatial navigation experience may produce structural changes in the hippocampus (e.g., Woollett & Maguire, 2011). Specifically, navigating complicated, novel routes daily has been linked to subsequent increases in hippocampal volume in London Taxi drivers (Maguire, Gadian, Johnsrude, Good, Ashburner, Frackowiak, & Frith, 2000). The same findings, however, have not been found in London bus drivers, who take the same, repetitive routes everyday (Maguire, Woollett, & Spiers, 2006). Thus, as organisms' locomotion and mobile range grow, so too do their hippocampi, but research suggests that the relation between experience and biology is bidirectional.

Measuring Spatial Cognition

Evidence of hippocampal involvement in spatial navigation and reorientation comes from three main types of studies. The first are lesion studies in which non-human animals, usually rodents, have a hole drilled into their hippocampus and their spatial behavior assessed (e.g., Hollup, Kjelstrup, Hoff, Moser, & Moser, 2001). These experimental studies allow researchers to determine the causal relationship between the hippocampus and spatial behavior by randomly assigning subjects to conditions in which they either have their hippocampi lesioned (i.e., experimental condition) or left intact (i.e., control condition). As such, researchers can assess the spatial abilities of their animal subjects before and after hippocampal damage.

Another way for researchers to examine the relation between the hippocampus and spatial skills is to conduct patient studies in which they test the spatial abilities of individuals with alzheimers, amnesia, brain damage specific to the hippocampus, or abnormal hippocampal development (Banta Lavenex, Colombo, Ribordy Lambert, & Lavenex, 2014; Meyer-Lindenberg, Hariri, Munoz, Mervis, Mattay, Morris, & Berman, 2005). These studies are typically done with adults, comparing the spatial abilities of individuals who are born with or develop hippocampal deficiencies to those with normal hippocampal functioning, all else (e.g., age, sex assigned at birth, overall brain volume, general intelligence) being equal. Similarly, some studies have examined the spatial reorientation skills of individuals with William Syndrome, a genetic abnormality that impairs hippocampal development (Eichenbaum & Cohen 2014). These studies have been done with participants ranging in age from early childhood (~5 years) to young adulthood (~30 years; Ferrara & Landau, 2015; Lakusta et al., 2010). Although they cannot be manipulated like lesion studies with non-human animals, these studies provide quasi-experimental evidence of the link between the hippocampus and spatial cognition.

Lastly, there are neuroimaging studies in which participants perform a spatial navigation or reorientation task in an MRI scanner and their hippocampal activation during task performance is subsequently assessed (e.g., Sutton et al., 2012). These studies allow researchers to assess hippocampal function via significant blood flow to that region during performance on a virtual task. Thus, researchers can infer whether the hippocampus would normally be active during spatial navigation and reorientation in the real-world. Because of the sensitive nature of functional MRI testing, requiring little movement and high levels of concentration from participants, these studies are typically

conducted with older children (~8 years+) and adults. Together, these three kinds of studies—animal, patient, and neuroimaging studies—shed light on the important role of the hippocampus in large-scale spatial cognition.

Overcoming Challenges to Measuring the Spatial Brain in Young Children

While it is known that spatial abilities develop rapidly during early childhood, less is known about the neurobiology of these changes. One of the major challenges to assessing brain development in relation to spatial cognition in young children is the lack of age-appropriate methods. One common technique often used to examine young children's brain activity is electroencephalography (EEG), which is relatively easy to use, but does not have the spatial resolution to measure subcortical regions like the hippocampus. In contrast, *fMRI* has better spatial resolution than EEG but is difficult to employ with very young children because the enclosed space of an MRI machine may elicit fear such as claustrophobia, and the tasks often used are too demanding of young children (e.g., requiring high levels of concentration while performing a task yet remaining still for a prolonged period). These issues may result in increased motion artifact, participant attrition, and, therefore, data loss (Poldrack, Paré-Blagoev, & Grant, 2002).

To overcome the challenges of using *fMRI* with young children, researchers may want to consider implementing shorter scan times, administering tasks during multiple, shorter visits to the lab as opposed to one long visit, keeping tasks performed in the scanner as simple as possible, and prioritizing the tasks of utmost relevance to the study earlier during the scan session. However, for children younger than 7, who may not be able to perform a behavioral task concurrently while lying still in the scanner, structural

MRI may be more suitable. When using structural MRI with young children, in which participants need not be awake or alert during the scan session, researchers may want to distract participants with a child-friendly movie.

As an alternative to MRI, recent research has employed a behavioral technique known as Pavlovian trace eyeblink conditioning (EBC) as a novel method to examine individual differences in hippocampal function in children as young as 3 years of age (Vieites et al., 2020). There are several compelling reasons to use EBC to examine children's hippocampal function (Vieites, Nazareth, Reeb-Sutherland, & Pruden, 2015). For one, EBC is a noninvasive, inexpensive procedure commonly used to study learning and memory of auditory and tactile associations. Secondly, it is relatively easy to implement with young typically- and atypically developing children (Reeb-Sutherland & Fox, 2015). Third, the underlying neural circuitry involved in EBC, which includes the hippocampus, has been well-established from both human and animal research (Jacobson, Stanton, Dodge, Pienaar, Fuller, Molteno, ... & Jacobson, 2011; Reeb-Sutherland & Fox, 2015; Christian & Thompson, 2003). For example, performance on trace EBC tasks relies on an intact hippocampal structure (Shors, Townsend, Zhao, Kozorovitskiy, & Gould, 2002) and is related to hippocampal function (Christian & Thomson, 2003; Cheng, Disterhoft, Power, Ellis, & Desmond, 2008; Plakke, Freeman, & Poremba, 2009; Kishimoto, Nakazawa, Tonegawa, Kirino, & Kano, 2006). Much like the hippocampus, trace EBC has a developmental trajectory, with rapid learning occurring between 4 and 6 years of age (Werden & Ross, 1972). Lastly, trace EBC responses are not related to general intelligence (Cromwell, Palk, & Foshee, 1961), making it a suitable measure for the study of discrete cognitive and behavioral processes such as spatial reorientation.

Conclusion

Although it is only an indirect measure of hippocampal function, EBC is a developmentally appropriate task that assesses the efficiency of learning and memory processes supported by the hippocampus. Thus, as the next study explores, EBC may be a simple yet valid proxy for studying hippocampal development in young children. Nevertheless, a combination of child-friendly neuroimaging, physiological, and behavioral techniques can help us acquire the most comprehensive understanding of the role hippocampal structure and function play in spatial cognition in early childhood.

STUDY II: RELATION BETWEEN HIPPOCAMPAL NEURITE DENSITY AND
TRACE EYEBLINK CONDITIONING IN FOUR- TO SIX-YEAR-OLD CHILDREN

ABSTRACT

Pavlovian trace eyeblink conditioning (EBC) may be a proxy for the efficiency and efficacy of hippocampal development across various learning and memory domains. Eyeblink conditioning is an associative learning task with a well-defined neural circuitry, including the hippocampus and cerebellum, and can be used non-invasively with pediatric populations, making it a potential tool for investigating brain network development. The current study examined relations between trace EBC and hippocampal and cerebellar volume and neurite density. Thirty-one 4- to 6-year-olds completed structural magnetic resonance imaging (MRI) and diffusion weighted imaging (DWI) scans and a trace EBC task. Using FreeSurfer, region-of-interest segmentation, and neurite orientation and density diffusion imaging (NODDI) reconstruction, average volume and neurite density was calculated for the bilateral hippocampus and cerebellum. The EBC training consisted of the presentation of a 750-ms pure tone followed by a silent 500-ms interstimulus trace interval followed by 100-ms air puff to the eye. Results revealed that greater neurite density, though not volume, of the bilateral hippocampus, but not of the cerebellum, predicted later onset of conditioned responses (CR), indicating more accurate anticipation of the air puff. Results suggest that maturation of hippocampal synaptic connections, captured by changes in neurite density, may engender resource-efficient differentiation of signal from noise in learned associations.

Keywords: trace eyeblink conditioning, EBC, hippocampus, structural magnetic resonance imaging, diffusion-weighted imaging

LITERATURE REVIEW

Introduction

The hippocampus of humans and non-human animals is a medial temporal lobe structure that plays a vital role in the formation of certain kinds of short- and long-term memories (i.e., spatial and declarative memory; Bird & Burgess, 2008). It is divided into the following subfields: dentate gyrus (DG), CA3, CA2, CA1, and subiculum. These hippocampal subfields show differential developmental trajectories, with the CA1 subfield of the hippocampus developing early, and the DG and CA3 subfields (Lavenex & Lavenex, 2013) showing more protracted development. Moreover, research in both animals and humans provides evidence that the hippocampus is not fully formed at birth but rather continues to grow and develop over time. In rats, for instance, the hippocampus may mature one to two months after birth (Altman & Das, 1965; Pokorny & Yamamoto, 1981). Furthermore, while human hippocampal synaptic connectivity matures at around 5 years of age (Seress, 2001), normal human hippocampal development may continue into early adulthood (Gogtay, Nugent, Herman, Ordonez, Greenstein, Hayashi, Clasen, Toga, Giedd, Rapoport, Thompson, 2006).

The protracted development of the hippocampus is then reflected in hippocampal-dependent behaviors, including spatial and episodic memory outcomes. Toddlers and young children, for instance, have greater difficulty than older children and adults recalling information (i.e., what, when, where) after a delay (i.e., forming episodic memories; Bauer, 2014) and combining landmarks with geometry to reorient themselves toward goal locations (Learmonth, Newcombe, Sheridan, & Jones, 2008; Twyman & Newcombe, 2010; Vieites, Pruden, Shusterman, & Reeb-Sutherland, 2020), suggesting

that the hippocampi of preschool children are not mature enough to process the demands of such tasks. However, children between the ages of 4 and 6 years improve considerably in their abilities to recall the details of events (Bauer, Pathman, Inman, Campanella, & Hamann, 2017; Drummey & Newcombe, 2002). Thus, it appears that the hippocampus undergoes a pivotal shift in development during the preschool and early-elementary school years—the very same period in which children begin to exhibit success on a variety of hippocampal-dependent tasks. While it is known that spatial and episodic memory abilities develop rapidly during early childhood, the neurobiology of these changes is less well-understood and has been understudied (Bauer, Pathman, Inman, Campanella, & Hamann, 2017). Thus, the details and nuances of how and whether children’s growing episodic and large-scale spatial memory abilities are directly related to the maturation of their hippocampi remain inconclusive.

Contributing to our lack of knowledge of young children’s hippocampal development in relation to their cognitive development is the lack of age-appropriate methods that may be used to examine hippocampal functioning. Popular techniques used to examine brain activity are either not suitable for examining subcortical structures or not ideal to use with young children. For example, while EEG can be easily implemented with children, it provides low spatial resolution and cannot be used to explore subcortical structures such as the hippocampus. *fMRI*, on the other hand, is an excellent technology for examining subcortical regions, but increased movement artifact and attrition in young children make it difficult to obtain valid data. Thus, when taking the high monetary cost of *fMRI* (>\$500/hour per participant) into consideration, using this method to examine real-time brain function in children younger than 5 years of age is not feasible. Thus, it is

vital to explore and develop other methods of data collection to practically study the behaviors that may be associated with hippocampal development in pediatric populations (Vieites, Nazareth, Reeb-Sutherland, & Pruden, 2015; Vieites et al., 2020). The present study attempts to overcome these methodological difficulties in gathering hippocampal function data by using a developmentally appropriate task that assesses the efficiency of learning processes supported by the hippocampus, namely Pavlovian eyeblink conditioning (EBC).

Measuring Hippocampal Function in Young Children Using Eyeblink Conditioning

Eyeblink conditioning is a relatively cost-effective technique commonly used to study associative learning and memory processes in both adult and pediatric populations. Generally, EBC entails learning the associations between auditory and tactile stimuli (Herbert, Eckerman, & Stanton, 2003). More specifically, during EBC, a conditioned stimulus (CS; e.g., tone) is paired with an unconditioned stimulus (US; e.g., puff of air to the eye) that naturally elicits a reflexive blink, or an unconditioned response (UR). When typically developing individuals are presented with several pairings, the tone CS alone comes to elicit a blink (i.e., conditioned response, CR). Two types of classical conditioning paradigms widely studied are trace eyeblink conditioning and delay eyeblink conditioning. In trace conditioning, the offset of the CS and onset of the US are separated by a silent “trace” period, whereas in delay conditioning, the CS and the US are presented in succession, but co-terminate (Cheng, Disterhoft, Power, Ellis, & Desmond, 2008). In both cases, the goal is to measure conditioned responses, or eyeblinks that occur after the offset of the CS (i.e., tone) but before the onset of the US (i.e., air puff).

Contingency detection, or the ability to identify the causal relations between events in the environment, is then crucial for the adaptation and survival of humans and other animals.

Eyeblink conditioning has been proposed to be a proxy for the efficiency of hippocampal development across different learning, memory, and spatial domains (Vieites et al., 2015, 2020). For one, it is non-invasive and can be employed in typical and atypical pediatric populations, making it an ideal tool for indirectly assessing brain function in young children (Vieites, et al., 2015). Secondly, the neural substrates of EBC have been consistently detected using both animal and human studies, with the cerebellum being implicated in both delay and trace conditioning, and the hippocampus being involved primarily in trace conditioning (Christian & Thomson, 2003).

Traditionally, studies have shown that animals with damage to their cerebellum show deficits acquiring conditioned, or learned, responses in both conditioning paradigms (Woodruff-Pak & Disterhoft, 2008), while animals with damage to their hippocampi exhibit greater difficulty learning during trace conditioning tasks (Beylin, Gandhi, Wood, Talk, Matzel, & Shors, 2001). Moreover, *fMRI* studies in humans report that the cerebellum is similarly activated during both conditioning paradigms, while the hippocampus, especially in the right medial temporal lobe, shows significantly greater activation during trace conditioning (Cheng et al., 2008). However, there are mixed findings on the importance of an intact cerebellum on trace conditioning, with studies showing that only damage to certain parts of the cerebellum, such as the cerebellar nuclei, impairs trace EBC performance (Gerwig, Kolb, & Timmann, 2007). Furthermore, unlike in rabbits, studies with mice, rats, and humans suggest that the cerebellar cortex is more critical for delay than for trace EBC (Woodruff-Pak & Disterhoft, 2008). Thus, while

earlier developing brain regions like the cerebellum may contribute to the ability to detect simple temporal contingencies, hippocampal maturity appears to be necessary only for relatively complex forms of associative learning.

Trace and delay conditioning have different developmental trajectories, and like spatial and episodic memory abilities, trace conditioning, specifically, exhibits a protracted developmental course. For example, in humans, delay conditioning is present very early after birth (Little, Lipsitt, & Rovee-Collier, 1984; Fifer, Byrd, Kaku, et al., 2010), while trace conditioning takes longer to develop, presumably due to the higher order cognitive abilities recruited during trace conditioning tasks (Herbert, Eckerman, & Stanton, 2003). Furthermore, typically developing preschool children ages 4 through 6 have shown greater difficulty acquiring trace than delay conditioning compared to typical adults, who do not display deficits in either procedure (Werden & Ross, 1972). These differences in developmental trajectories between the two paradigms may occur since trace, but not delay, conditioning requires a “memory trace” to link the CS and the later US (Gerwig, Kolb, & Timmann, 2007), thus complicating the task for infants and young children. Furthermore, these results indicate that the neural substrates, including the hippocampus, crucial for learning trace conditioned responses may be undergoing a pivotal shift in growth and development around 4-6 years of age.

Eyeblink conditioning, however, does not allow for the direct examination of underlying brain regions. Hence, brain imaging continues to be the gold standard for studying the neural basis of spatial and episodic memory. For instance, structural MRI, a more feasible imaging technique than *fMRI*, can be used to evaluate hippocampal structural components such as hippocampal subfield volume size (measured with high-

resolution T1- and T2-weighted structural MRI) and neurite density (measured by neurite orientation dispersion and density diffusion weighted imaging; NODDI-DWI).

Furthermore, unlike with *f*MRI, an individual does not have to remain awake and active in the scanner to be assessed, making structural MRI an ideal tool to study the brain anatomy of young children in relation to behavioral measures.

The Current Study

While structural MRI is a useful tool for studying the weight and composition of neural regions, the method does not directly access hippocampal *function*, which raises challenges for exploring how individual differences in hippocampal function relate to behavioral performance. Moreover, although there is much evidence that the hippocampus underlies learning and memory in non-human animals and human adults, there remains a paucity of data on the relations between hippocampal structure, especially with respect to neurite density, and associative learning in pediatric populations. However, to gain a richer sense of the underlying neural processes of learning and memory domains, it is important to explore not only the size of brain regions, but the connections and proliferation of neuronal axons and dendrites (i.e., neurite density). Thus, as a first step to validate the use of EBC as a proxy for hippocampal development, the current study examined the relations between performance on a trace EBC paradigm (i.e., the offset of the conditioned stimulus and onset of the unconditioned stimulus are separated by a silent trace period) and hippocampal and cerebellar volume and neurite density.

Aim one assessed whether hippocampal volume predicted EBC performance (i.e., % CRs, timing of CRs) when controlling for age, sex assigned at birth, socioeconomic

status (SES; maternal education was used as a proxy for SES), and average intracranial volume. I predicted that greater hippocampal volume (particularly right hippocampal volume), but not cerebellar volume, would be associated with greater CRs (i.e., learning) during the trace EBC task. Aim two evaluated whether hippocampal neurite density predicted EBC performance when controlling for age, sex assigned at birth, SES, and average cortical neurite density index (NDI). Since the method for acquiring neurite density is relatively novel, research findings about the relation between neurite density and behavior are uncommon, and few, if any, studies have investigated neurite density in early human hippocampal development in relation to behavioral performance on learning and memory tasks. However, a “neural efficiency” hypothesis (Dunst, Benedek, Jauk, Bergner, Koschutnig, Sommer,... & Neubauer, 2014; Haier, Siegel, Bang, Abel, & Buchsbaum, 1992) would suggest that greater neural pruning is associated with better functioning and efficiency of neural transfer. Hence, if this neural efficiency model is correct, then I would predict that reduced hippocampal neurite density would be associated with greater and faster learning on the trace EBC task, while cerebellar neurite density would not be related to EBC performance.

METHOD

General Procedure

A single visit to the laboratory took approximately three hours, but for the current study, the following tasks took roughly 60 minutes to complete. After parents filled out their consent and MRI screening forms, children completed a: (1) T1-weighted structural scan; (2) a T2-weighted structural scan; (3) a Diffusion Weighted Imaging (DWI) scan (3T; 102 diffusion directions); and (4) a 15-minute trace eyeblink conditioning (EBC)

task. Since the current study is part of a larger study comprised of one neuroimaging and several behavioral tasks, and because the neuroimaging task might be most sensitive for children, the MRI scans were administered first to avoid as much attrition as possible on the neuroimaging variable.

Participants

Participants consisted of typically developing children (N=31; 14 Girls; *Mage*=5.67; *SD*=0.89) ages 4 (N = 11; 4 Girls; *Mage* = 4.61; *SD* = 0.16), 5 (N = 7; 4 Girls; *Mage* = 5.73; *SD* = 0.09), and 6 (N = 13; 6 Girls; *Mage* = 6.53; *SD* = 0.31) years living in Broward and Miami-Dade counties. Participants were recruited via emails to local listservs, through flyers handed out and prospective participant contact information collected at family-friendly events around town, and from a pool of parents and children who previously participated in developmental studies at the University. Participants reflected the racial and ethnic demographics of the surrounding region of Miami, consisting of 42% Hispanic, 13% African American or Black, 6% White non-Hispanic, and 39% mixed race or another ethnicity. The children's mothers were well educated, with 48% completing an undergraduate college degree, 39% completing a graduate or professional degree, 7% completing a high school degree, and 6% completing at least some college (e.g., Associate degree).

Measures

Structural Magnetic Resonance Imaging: Scanning children as young as 4-years requires a special protocol (Byars, Holland, Strawsburg, Bommer, Dunn, Schmithorst, & Plante, 2002), such as specialized movement training and habituation to MRI sounds during a carefully managed 25-minute preparatory phase. During the pre-MRI phase,

children were shown a 5-minute video teaching them what MRI does and demonstrating the procedure with a young child. Afterward, children participated in a brief “mock” scan, where they were pre-exposed to the conditions of the real scanner but in a separate room. During the mock scan, children were asked to lie down still “like a statue” in a pretend scanner while wearing headphones and head gear like that used in the real scanner. To show the child the task was not harmful, the experimenter asked an assistant to demonstrate playing “the statue game” first. While inside the mock scanner, children were asked not to move or cross their hands and feet while they listened to different kinds of noises they would hear in the real scanner. They were told that whenever they heard the unusual sounds, that meant that the machine was taking a picture of their brain, so they ought to lie still to avoid having a “blurry” picture taken. The preparatory phase was done to assess whether children might feel shock, unusual discomfort, or claustrophobia in the real scanner as well as to prevent presenting the child with any unpleasant surprises in the real scanner. Out of 40 scans attempted, nine children refused to participate either during the mock session or right before the real session began and one other child could not complete the full session because they arrived late, leaving 31 viable participants with volumetric data and 30 viable participants with DWI data.

After the mock scan, an MRI technician reviewed the participant’s MRI screening form and interviewed their parent(s) about their child’s medical history or any issues/objects (i.e., surgeries, metal ear tubes, band aids) that may interfere with the child’s ability to be safely scanned. Next, the parent took their child to use the restroom and had them change into MRI-safe scrubs. After the MRI technician cleared the child for scanning, they, along with an experimenter, brought the child into the main MRI

room, removed the child's shoes, and fitted them with a hair net before positioning them on the scanner's bed with the appropriate head gear. Children wore blankets and watched a child-friendly movie of their choice during a 30–35-minute session. The experimenter monitored the child through a window in the technician's room and could hear and speak to the child through speakers whenever necessary (e.g., to remind the child not to move their head). If participants refused to perform the scan without a parent by their side, then one parent, after careful screening, could sit in the MRI room wearing headphones during their child's session. In such cases, the parent was given explicit instructions not to touch their child and only to talk to their child when absolutely necessary while the scan was in session.

Diffusion-weighted images, which reveal information about the diffusion of water in different cellular environments and the connectivity between brain regions, were acquired on a 3T scanner, $b=500, 1000, 2000, 3000$, $1.7 \times 1.7 \times 1.7$ mm voxel size with 102 directions. T1- and T2-weighted images were acquired to facilitate DWI images post-processing. To provide a semiautomated segmentation of subcortical structures and an estimate of intracranial volume, two-dimensional surface renderings of each participant's T1-weighted scans were constructed in FreeSurfer v6.0. Volume of subregions (in mm^3) was estimated from these segmentations by voxel count (3D volume pixels) within the Region-of-Interest (ROI), namely the hippocampus and cerebellum. With the microstructure diffusion toolkit (MDT), neurite orientation and density diffusion imaging (NODDI) reconstruction was accomplished using the T2- and diffusion scans. The NODDI model provided an intraneurite volume fraction (INVF) metric, which in grey matter is an indicator of dendritic and axonal density. Using the FreeSurfer ROI

segmentation, average neurite density was calculated for the bilateral hippocampus and cerebellar cortex.

Eye-blink Conditioning Paradigm: The procedure used to measure associative learning was a trace EBC paradigm (See Figure 1A) like that used by Jacobson and colleagues (Jacobson, Stanton, . . . & Jacobson, 2011). Children participated in a 15-minute session in which they were presented with paired auditory (i.e., tone) and tactile (i.e., air puff) stimuli while their eyeblink responses were measured (See Figure 1B). Stimulus presentation, data collection, and data processing were completed using a commercially available human eyeblink conditioning system (San Diego Instruments, San Diego, CA). During the task, children were fitted with a soft headband, which was attached to an infrared emitter-sensor that recorded their eyeblink responses and tubing that delivered the air puffs. The sensor and tubing were positioned approximately 2 inches away from the child's left eye. Tones were delivered through external speakers, which were positioned approximately 12 inches away from each side of the child's head.

Children were told that they were going to feel light puffs of air to their left eye and that they would hear sounds regularly. Before beginning, an experimenter delivered a few test puffs of air to their own eye and then to the child's arm to demonstrate to the child that the procedure would not be painful. For the duration of this task, children sat in a dimly lit room facing a television monitor, which played a silent, child-friendly movie or show of their choice. Parents could remain in the room with their child during the procedure but were instructed to remain as quiet as possible and not to interact with the child. Out of 40 children who participated in the larger study, one child refused to

complete the EBC task. However, that child also refused to participate in the MRI session, so they were excluded for the current study.

Trace EBC training consisted of 80 tone-puff trials (i.e., presentation of a 750-ms tone CS, an 80 dB, 1000 Hz pure tone, followed by a 500-ms interstimulus trace interval during which no stimulus was presented, followed by a 100-ms air puff US, ~10 lb/in²), 10 tone-alone trials, and 10 puff-alone trials. Learning via conditioned responses (CR) was defined as eyeblinks that occurred between 800 and 1300-ms after the onset of the tone during the tone-puff paired trials and after 800-ms during the tone-alone trials. CR onset latency, or the average latency (ms) to which the child started their blink, was computed across all tone-puff and tone-alone trials (90 trials).

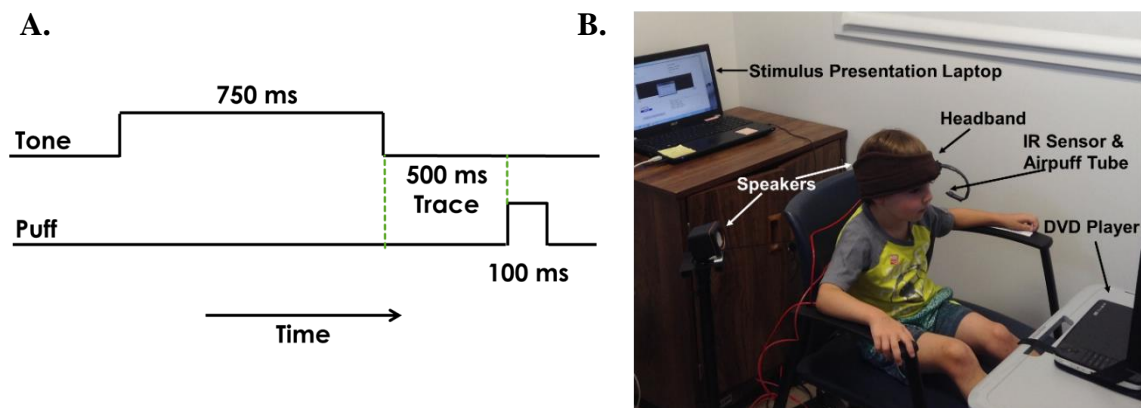


Figure 1. Trace EBC paradigm depicting timing of the CS, trace period, and US (A) and EBC setup (B). Panel B shows a young child facing a DVD player while wearing a headband with a sensor pointing toward their left eye. The sensor delivers the air puffs and measures blink responses. One speaker is positioned on each side of the child's head.

RESULTS

Independent samples t-tests showed that there were no gender differences in overall learning ($t(36) = -0.024$; $p=.981$) or onset of learning ($t(36) = -0.578$; $p=0.567$). There were no floor or ceiling effects as performance was variable across all tasks. Table

1 demonstrates the descriptive statistics for each variable, separated by participant sex assigned at birth. Pearson's bivariate correlations revealed that age was significantly, positively related to associative learning via CRs, but only during tone-alone trials ($r=0.390$; $p=0.016$). Children's percentage of CRs across tone-alone trials was also significantly, positively correlated with when, on average, they began their conditioned blinks (in milliseconds) during tone-puff and tone-alone trials (i.e., 90 trials; $r=0.478$; $p=0.002$). Moreover, left cerebellar neurite density (NDI) was significantly, negatively correlated with learning during tone-alone trials. Table 2 demonstrates the bivariate Pearson's correlations between age at visit, learning (i.e., % CRs during tone-alone trials), onset of learning (i.e., CR start time in ms), left and right hippocampal volume, and left and right hippocampal and cerebellar NDI.

Variable	<u>Girls</u>		<u>Boys</u>		<u>All</u>			
	<i>M(SD)</i>	<i>n</i>	<i>M(SD)</i>	<i>n</i>	<i>M(SD)</i>	<i>n</i>	Min	Max
Age at Visit	5.78 (0.87)	14	5.58 (0.92)	17	5.67 (0.89)	31	4.30	6.99
Learning (i.e., % CRs during tone-alone trials)	45.32 (29.51)	14	47.65 (25.05)	17	46.59 (26.71)	31	0	90
Onset of Learning (ms)	1075 (92.04)	14	1091 (81.60)	17	1084.09 (85.38)	31	881.50	1272.56
Left Hipp. Volume	3449 (388)	14	3883 (397)	17	3687.05 (444.23)	31	2653.80	4569.00
Right Hipp. Volume	3593 (381)	14	4040 (343)	17	3837.86 (420.49)	31	2927.60	4544.20
Intracranial Volume	1.3M (100K)	14	1.5M (142K)	17	1.4M (150K)	31	1.1M	1.7M
Left Hipp NDI	.26 (.07)	14	.25 (.06)	16	.25 (.06)	30	.09	.33
Right Hipp NDI	.26 (.07)	14	.25 (.06)	16	.25 (.06)	30	.08	.33
Left Cerebellar NDI	.42 (.08)	14	.41 (.06)	16	.42 (.07)	30	.21	.48
Right Cerebellar NDI	.42 (.08)	14	.42 (.07)	16	.42 (.07)	30	.20	.48
Average Cortical NDI	.38 (.07)	14	.37 (.06)	16	.37 (.06)	30	.21	.46

Table 1. Means and Standard Deviations of Variables by Participant Sex Assigned at Birth. Sex assigned at birth was dummy coded as 0 for girls and 1 for boys.

	1	2	3	4	5	6	7	8	9
1. Age	-								
2. Learning	.390*	-							
3. Onset of Learning	.308	.478**	-						
4. Left Hipp Volume	.040	.160	.281	-					
5. Right Hipp Volume	.055	.201	.267	.906**	-				
6. Left Hipp NDI	.237	-.141	.127	-.178	-.146	-			
7. Right Hipp NDI	.204	-.192	.091	-.172	-.149	.985**	-		
8. Left Cer NDI	.028	-.383*	-.145	-.218	-.223	.870**	.882**	-	
9. Right Cer NDI	.055	-.355	-.095	-.163	-.180	.876**	.890**	.988**	-

*Table 2. Pearson's Bivariate Correlations between Age at Visit, Learning (i.e., % CRs during tone alone trials), Onset of Learning (i.e., CR start time in ms), Bilateral Hippocampal Volume, and Bilateral Hippocampal and Cerebellar Neurite Density (NDI) ***Denotes $p < 0.001$; **Denotes $p < 0.01$; *Denotes $p \leq 0.05$*

The first aim of the current study examined whether hippocampal size (i.e., volume) predicted EBC performance (i.e., % CRs, timing of CRs) when controlling for age, sex assigned at birth, socioeconomic status (SES; maternal education was used as a proxy for SES), and average intracranial volume. However, multiple linear regression analyses showed that hippocampal volume did not predict performance on the EBC task, whether it was measured via onset of learning (i.e., CR start time; $p=0.612$ for left side; $p=0.703$ for right side), learning (i.e., % CRs) across all tone-puff paired and tone-alone trials (i.e., 90 trials; $p=0.830$ for left side; $p=0.718$ for right side), or learning across just tone-alone trials (i.e., 10 trials; $p=0.614$ for left side; $p=0.194$ for right side).

The second aim of the current study was to assess whether hippocampal neurite density, that is the directionality and connectivity of white matter, rather than overall hippocampal size predicted EBC performance. Robust linear regressions revealed that while controlling for age, sex assigned at birth, SES, and average cortical NDI, greater neurite density of the left ($B=1724.81$; $p=0.003$; adjusted $R^2 = 0.30$; See Figure 2A) and right ($B=1603.56$; $p = 0.008$; adjusted $R^2= 0.24$; See Figure 2B) hippocampus predicted higher CR onset latency. However, neither left ($B=-38.82$; $p = 0.96$; adjusted $R^2 = -0.025$; See Figure 2C) nor right ($B=313.97$; $p = 0.61$; adjusted $R^2 = -0.014$; See Figure 2D) cerebellar cortical neurite density predicted CR onset latency. Furthermore, bilateral hippocampal neurite density did not predict learning across all 90 paired and tone-alone trials ($p=0.130$ for left side; $p=0.167$ for right side) or across the 10 tone-alone trials ($p=0.755$ for left side; $p=0.782$ for the right side).

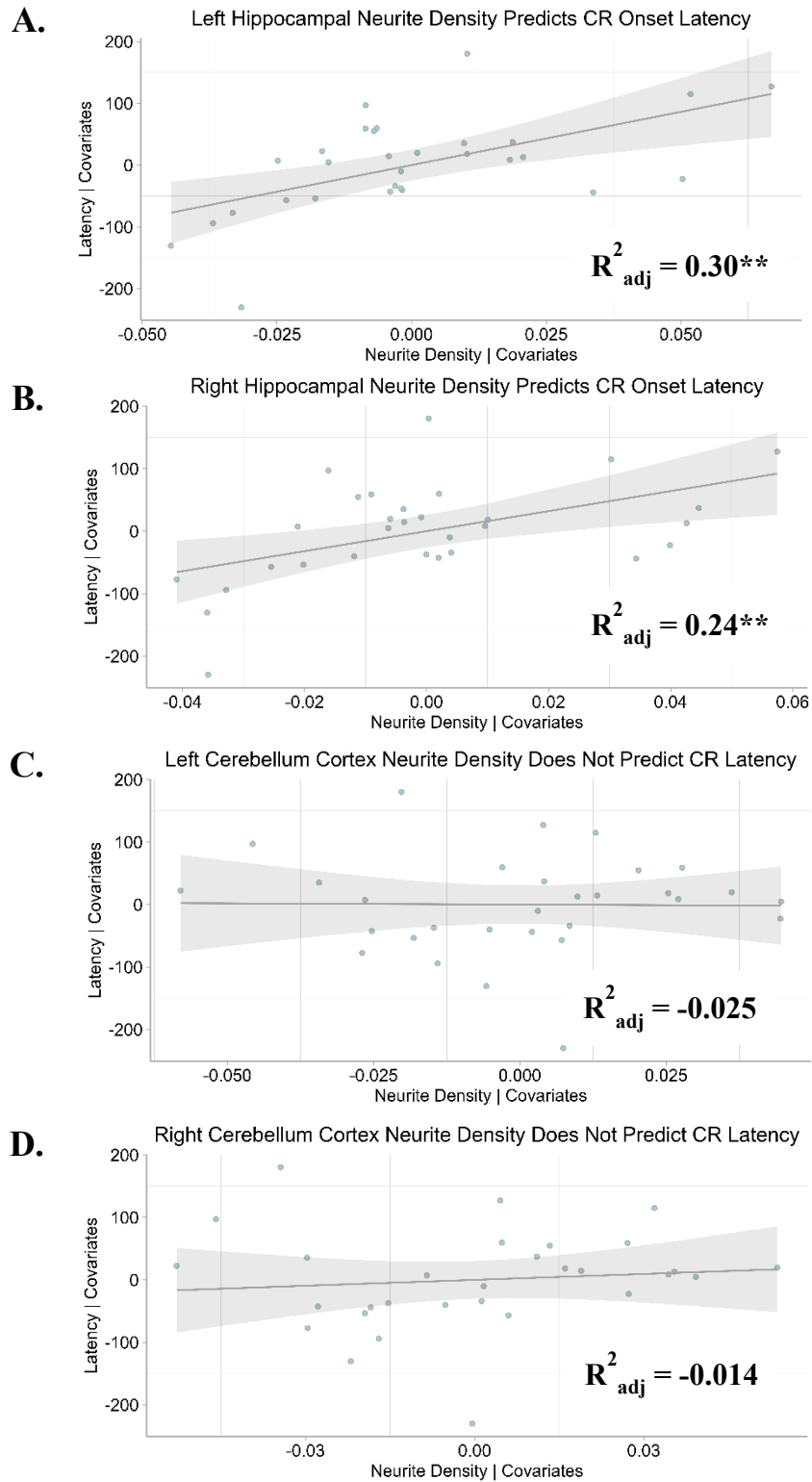


Figure 2. Robust linear regression plots with 95% CI for EBC latency as a function of left (A) and right (B) hippocampal NDI and left (C) and right (D) cerebellar NDI.

DISCUSSION

Considering the special challenges to obtaining neural correlates of behavior in preschool- and early elementary school-aged children, the current study sought to assess the validity of using a hippocampal-dependent EBC paradigm as a proxy for hippocampal efficiency and development. Aim one assessed the relations between 4-6-year-old children's associative learning skills, as measured by their conditioned blinks and the timing of those blinks on a trace EBC task, and the size (i.e., volume) of their hippocampi. Aim two then evaluated the relations between children's associative learning abilities and, more specifically, their hippocampal neurite density, as measured by neurite orientation dispersion and density diffusion weighted imaging (NODDI-DWI). Many studies on EBC focus on the overall acquisition of conditioned learning, but the current study investigated the neural correlates of both the acquisition and timing of learned responses (i.e., CRs). Moreover, studies have rarely, if ever, examined neurite density in young children in relation to behavioral performance on learning and memory tasks, and while studies on associative learning in pediatric populations commonly use a standard delay conditioning paradigm, the current study evaluates both neurite density and trace EBC performance in a sample of pre-school- and early elementary school-aged children.

While hippocampal volume was not associated with any of the EBC measures, greater bilateral hippocampal neurite density predicted later onset of learned associations on the EBC task. In other words, children with greater left and right hippocampal neurite density blinked closer to the US (i.e., air puff) than children with less hippocampal neurite density, indicating that rich hippocampal connectivity may have helped children accurately time their blinks in anticipation of the air puff. This finding, however, was not

present when examining either bilateral cerebellar volume or neurite density. Curiously, while animal studies have found that cerebellar structures can enhance trace EBC responses (Gruart, Guillazo-Blanch, Fernández-Mas, Jiménez-Díaz, & Delgado-García, 2000), the current study found that left cerebellar neurite density was significantly, negatively correlated with associative learning during tone-alone trials. Perhaps cerebellar pruning is associated with increased acquisition of learned responses during trace EBC. However, cerebellar lesion studies with humans have found that while damage to the cerebellar nuclei significantly impaired trace conditioned learning, damage to the cerebellar cortex did not (Fortier, Disterhoft, & McGlinchey-Berroth, 2000), especially when compared to delay conditioning performance (Gruart, Guillazo-Blanch, Fernández-Mas, Jiménez-Díaz, & Delgado-García, 2000). Together, these findings suggest that while the cerebellum may not be completely uninvolved in trace conditioning, it may not be as critical for optimal trace EBC performance as the hippocampus.

It is worth noting that the current study is only correlational, lacks a comparison group of atypically developing children and, thus, does not provide any causal evidence that hippocampal development predicts associative learning abilities in young children. Hence, future studies may want to compare hippocampal-dependent EBC between samples of children with hippocampal abnormalities, such as those with Williams Syndrome, and those with typical hippocampal development. Secondly, the current study does not measure EBC performance simultaneously with hippocampal function (e.g., *fMRI*). Thus, it is not clear whether children's hippocampi were significantly activated compared to their cerebellums while they performed the EBC task. Thirdly, the current

study only uses one kind of conditioning paradigm, so future work should consider including a comparison of trace and delay EBC when investigating the neural correlates of associative learning, especially if both the hippocampus and cerebellum are of interest. Lastly, the number of children with viable MRI data in this study was relatively scant, so a larger sample size may have yielded significant results that were not present (e.g., between overall learning and hippocampal volume or NDI).

Studies on EBC have focused mainly on the acquisition of CRs, with little attention paid to CR timing. However, the timing of eyeblinks is critical to normal acquisition of learned associations (Boneau, 1958; Ebel & Prokasy, 1963) because the purpose is to blink just prior to the onset of the US so that the eye is closed and thus protected from the air puff (Gerwig et al., 2007). Yet individuals with cerebellar abnormalities, such as those with autism, show earlier timing of CRs on a delay conditioning task compared to typically developing individuals. In addition, Gerwig and colleagues (2005) found that patients with cortical cerebellar degeneration, but not all types of cerebellar damage, displayed earlier CR onset latencies on a standard delay EBC paradigm than age-matched controls (Gerwig, Hajjar, Dimitrova, Maschke, Kolb, Frings, ... & Timmann, 2005). However, the current study did not find a relation between the cerebellum and EBC performance, perhaps because a delay conditioning task was not used. Results suggest that maturation of hippocampal synaptic connections, captured by changes in neurite density with age and experience, may allow children to efficiently differentiate signal from noise when learning associations in the environment. As such, trace EBC may be a novel yet simple proxy for investigating hippocampal development in young children as well as individuals with hippocampal and memory impairments.

STUDY III: DOES UNDERSTANDING BASIC RELATIONAL LANGUAGE HELP
CHILDREN SUCCEED ON A SPATIAL REORIENTATION TEST?

ABSTRACT

Humans often use spatial language as a means of describing, representing, and understanding their environments, which helps them plan successful navigational strategies. Spatial language includes words that describe relations between objects, as well as words that describe the features and properties of objects in space. The current study investigated individual differences in children's knowledge of basic generic relational terms (e.g., nearest, across, in front) and more specific directional words (e.g., left, right) in relation to their choices on a spatial reorientation test. Thirty-nine 4- to 6-year-old children (19 girls) completed a spatial reorientation test, a left-right assessment, the Boehm-3 Preschool Test of Basic Concepts, the Children's Mental Transformation Task (CMTT), and the NIH Toolbox Pattern Comparison Processing Speed (PCPS) Test. Multiple regression analyses revealed that when controlling for age, CMTT scores, and PCPS scores, children who knew right from left were better at encoding the geometry (i.e., shape) of a room when solving a spatial reorientation task. Children's performance on the Boehm-3, however, did not predict their landmark or geometry use when controlling for age and other cognitive abilities. These findings suggest that, independent of age, children's understanding of specific spatial concepts and not necessarily relational language more broadly may help them find their bearings when lost, demonstrating that psychological constructs like language are linked to spatial cognition in early childhood.

Keywords: spatial language, relational and directional terms, spatial reorientation, navigation, relative frames of reference

LITERATURE REVIEW

Introduction

We often use language to describe, cognitively represent, and understand the space around us to help us successfully navigate it. This type of language, known as spatial language, includes words that describe relations between objects or between the self and objects (e.g., across, below, around, near, left) as well as words that describe the features and properties of objects (e.g., big, tall, round) in space (Pruden, Levine, and Huttenlocher, 2011). We may talk about how things in the environment are related using different systems of spatial localization, including intrinsic (e.g., they are *in front* of the house), relative (e.g., they are to the *left* of the house), and absolute (e.g., they are *north* of the house) frames of reference (Ishikawa, 2020). Individuals vary in the types of spatial localization systems they prefer to use when navigating and reorienting themselves, but the languages they speak may be intimately linked to the way they encode and describe spatial relations (Ishikawa, 2020; Shusterman & Li, 2016).

Levinson (1996) found that unlike Dutch participants, whose language commonly uses relative expressions (e.g., right) when describing spatial relations, the language of the Tenejapa participants of southern Mexico lacks relative spatial descriptions. Furthermore, these cultural differences in linguistic encoding of spatial relations manifested in different outcomes on a spatial task asking participants to place an arrow in the original orientation of a spatial array after their perspective was changed, whereby the Dutch participants tried to solve the task using their understanding of left and right directions while the Tenejapa participants (more successfully) solved the task using their knowledge of cardinal directions (e.g., south) (Ishikawa, 2020). Moreover, in one study,

young children used the language they heard that described object properties, such as their colors and locations/directions (e.g., the red square is on the left), to help them find a target object in an array after a delay (Dessaegn & Landau, 2008). Hence, if language is a useful tool for thinking and talking about what we see in the world, then it may support our spatial abilities.

How Language May Facilitate Spatial Abilities

Experimental, correlational, and cross-cultural research suggests a possible causal link between language and spatial cognition, whereby the former facilitates the latter (Gentner, Özyürek, Gürcanli, & Goldin-Meadow, 2013; Loewenstein & Gentner, 2005; Miller, Patterson, & Simmering, 2016; Pyers, Shusterman, Senghas, Spelke, & Emmorey, 2010). For example, Hermer-Vazquez and colleagues (1999) found that adults who performed a verbal shadowing task that required them to repeat words as they heard them via an audio recording while trying to reorient using a large feature (i.e., red wall) in a small, rectangular enclosure were not able to locate the hidden object at above chance levels without access to lexical resources. These findings suggest that spatial language may be crucial at least when learning a novel spatial task. Nevertheless, while previous studies have found positive associations between language and spatial cognition, there remains a paucity of data on the relations between children's knowledge of spatial language and their large-scale spatial skills (i.e., navigation, reorientation) while accounting for age and other spatial and general cognitive abilities.

One argument for why language is so important for the development of spatial abilities posits that having a richer grasp of spatial language in general translates to paying more attention to the spatial world and, thus, better performance on spatial tasks

(Pruden et al., 2011). For example, Pruden and colleagues (2011) found that the more spatial words children produced at 14-46 months, the better they performed on small-scale spatial tests (e.g., mental rotation tasks) at 54 months of age. On the other hand, some scholars argue that it is knowledge of specific, task-relevant words rather than more spatial language that predicts, or at least correlates with, performance on those tasks (Miller, Vlach, & Simmering, 2017; Shusterman, Lee, & Spelke, 2011). For example, Miller and colleagues (2017) found that children's adaptive use of task-relevant language—that is, how often they produced relevant versus irrelevant cues (even if non-spatial) when describing a spatial scene—facilitated their spatial performance above and beyond the quantity of spatial words they produced. I test both hypotheses in the current study, which aims to explore individual differences 4- to 6-year-old children's knowledge of specific directional (e.g., left and right) words and more general relational (e.g., near, around, in front) terms in relation to their choices on a spatial reorientation test.

Spatial words such as *front*, *left*, and *north*, for example, can be used to solve spatial tasks. Some words, however, are more relevant for understanding and completing certain tasks than others. Research on the relations between language—specifically, words that describe the spatial world—and spatial cognition suggests that the latter depends on the acquisition of certain kinds of spatial terms (i.e., directional terms like left and right; Pyers, Shusterman, Senghas, Spelke, & Emmorey, 2010). Pyers and colleagues (2010) studied two cohorts of deaf individuals who learned an emerging Nicaraguan sign language at the same age but a decade apart. The researchers found that the second cohort of signers, having acquired a richer and more complex form of the language, used left-right spatial relations more consistently than the first cohort. Furthermore, the second

cohort outperformed the first cohort on two spatial tasks requiring the participants to use a landmark in a rectangular room to locate a hidden object after being disoriented in one condition and remaining stationary but having the room rotated in another condition (Pyers et al., 2010). In addition, the absence of spatial language in a sample of deaf children who were not exposed to sign language coincided with relatively poor performance on a non-linguistic, Spatial Mapping Task compared to hearing children (Gentner, Özyürek, Gürcanli, & Goldin-Meadow, 2013). Taken together, these studies suggest that spatial language facilitates spatial cognition rather than strictly being a linguistic tool that develops from spatial experience.

Developmental work on the ability to reestablish one's sense of direction after being lost or disoriented, known as spatial reorientation, suggests that spatial language may serve as an egocentric, or body-centered, frame of reference (Newcombe et al., 2013) by which children can combine geometric (i.e., lines, distances, angles, shapes) and landmark (i.e., salient environmental features) information to reorient themselves toward goal locations (Hermer-Vazquez, Moffet, & Munkholm, 2001; Hermer-Vazquez, Spelke, & Katsnelson, 1999; Shusterman & Spelke, 2005). Specifically, it has been proposed that children's shift from reorienting by geometric to landmark cues is due to the emergence of spatial language (i.e., specifically, comprehending the difference between left and right) at around 6 years of age (Hermer-Vazquez et al., 2001; Shusterman & Spelke, 2005). For example, 4-year-old children who were trained and learned how to distinguish between right and left exhibited better performance on a spatial reorientation test than children who did not understand right from left (Shusterman & Spelke, 2005). Furthermore, children between the ages of 6 and 11 years of age who were most adept at

understanding spatial locative terms (i.e., below/above, in/out, near/far, up/down, in front of/behind, from/to, and between) performed better than children who had relatively poor receptive spatial grammar skills on a landmark-based navigation task requiring them to learn a pathway after a delay and subsequently represent it on a map (Piccardi, Palermo, Bocchi, Guariglia, & D'Amico, 2015). Altogether, these findings suggest that when children begin to understand the concepts of spatial locations and directions, they improve in their abilities to find desired locations, at least with the aid of landmarks.

The Current Study

Notably, there are a multitude of factors—from brain development to language acquisition to spatial experience—that interact to contribute to the development of spatial skills in young children. The present study analyzed psychological and conceptual correlates of spatial cognition, focusing on spatial relational language since it is the kind of spatial language commonly used when devising navigational strategies. Specifically, I explored the relations between children's spatial language comprehension and their spatial reorientation outcomes. I focused on intrinsic (e.g., in front, on top) and relative (e.g., left) ways of talking about space because I suspected these concepts would be easier for young children to grasp than absolute, or geocentric, references (i.e., north). However, it is worth noting that the degree of use and existence of certain frames of reference vary from one language community to another (Li, Abarbanell, Gleitman, & Papafragou, 2011).

Aim one of the current study explored children's knowledge of directional words (e.g., left, right) relative to their spatial reorientation abilities. I predicted that children's understanding of directional terms would be associated with their increased ability to

combine the geometric and landmark information in a room by choosing the correct corner on a spatial reorientation test. Aim two examined the relation between children's knowledge of basic relational words (e.g., near, around, in front) and their spatial reorientation performance. I predicted that children's understanding of these general relational terms would be associated with their increased ability to combine geometry and landmark information to correctly locate a hidden object after being disoriented.

METHOD

General Procedure

A single visit to the laboratory took approximately 60 minutes. After parents gave their consent, children participated in five tasks: a spatial reorientation test, an assessment of left and right knowledge, the Boehm-3 Preschool Test of Basic Concepts, a mental rotation test designed for young children, and a processing speed test. I administered the spatial reorientation test first given the logistics of the preparation and organization of the room before participants arrived (e.g., closing curtains, turning on lights and noise cancelling machines) and because it was my main outcome measure of interest. The spatial reorientation task was followed by the left-right assessment, the Boehm-3 test, the mental rotation test, and, lastly, the processing speed test. I administered the left-right assessment directly after the spatial reorientation test because it was a quick and simple task that could be completed in under one minute and because I did not want to remind children of their left and right directions inadvertently before performing the spatial reorientation test as this could influence their performance. I administered the mental rotation and processing speed tests last because they were control measures, and I did not expect them to meaningfully relate to any of my primary measures of interest.

Participants

Participants consisted of typically developing children (N=40; 19 Girls; Mage = 5.56; SD = .85) ages 4 (N = 16; 7 Girls; Mage = 4.64; SD = 0.19), 5 (N = 10; 5 Girls; Mage = 5.68; SD = 0.21), and 6 (N = 14; 7 Girls; Mage = 6.51; SD = 0.31) years living in Broward and Miami-Dade counties. Participants were recruited via emails to local listservs, through flyers handed out and prospective participant contact information collected at family-friendly events around town, and from a pool of parents and children who previously participated in developmental studies at the University. Participants reflected the racial and ethnic demographics of the surrounding region of Miami, consisting of 45% Hispanic, 10% African American or Black, 5% White non-Hispanic, and 40% mixed or another ethnicity. The children's mothers were well educated, with 47.5% completing an undergraduate college degree, 40% completing a graduate or professional degree, 7.5% completing a high school degree, and 5% completing at least some college.

Measures

Spatial Reorientation Test: The spatial reorientation task was like that used by Vieites and colleagues (2020). Children were tested in an 8' x 11' room with an 18" high, 4' by 6' inner enclosure (See diagram of room in Figure 1A). The main purpose of the inner enclosure was to restrict children's locomotion, which studies have shown increases the difficulty of the task (for a review, see Chiandetti & Vallortigara, 2008), thus reducing the chance of obtaining little variability in performance (i.e., ceiling effects). Three of the curtain-covered walls of the larger space were white and one wall was red, serving as the cue to the location of the hidden toy. Identical floor lamps were placed at

each corner of the larger space, and opaque boxes, one of which contained the hidden toy, were placed at the corners of the smaller space so that the four corners of the testing room were indistinguishable to the child. In addition, noise cancelling machines were placed behind the two long curtains. A ceiling, constructed from blue fabric, hung from wall to wall to eliminate any external ceiling cues. Thirty participants were administered the task in this manner; nine participants were administered the task without the blue fabric or metal wires when the room was reconstructed with new sliding curtains hanging from a train on the ceiling. The inner barrier, lamps, toy chests, and noise cancelling machines remained the same for all 39 participants.

After the child was escorted into the testing room (See Figure 1B), they watched as the experimenter placed a small toy inside one of the boxes closest to the red wall. Next, the experimenter disoriented the child by blindfolding and spinning them around in circles until the child was unable to identify where the door of the room was located. Disorientation normally took 20-25 full rotations. After the disorientation procedure, the child's blindfold was removed, and they were encouraged to point to the location of the hidden toy. The corners in which the toy was hidden and the direction the child faced after disorientation was predetermined across 8 trials. Children were congratulated if their first choice was correct, but if they chose the wrong box, then they were immediately shown the correct location of the toy. The spatial reorientation test took approximately 15 minutes to complete.

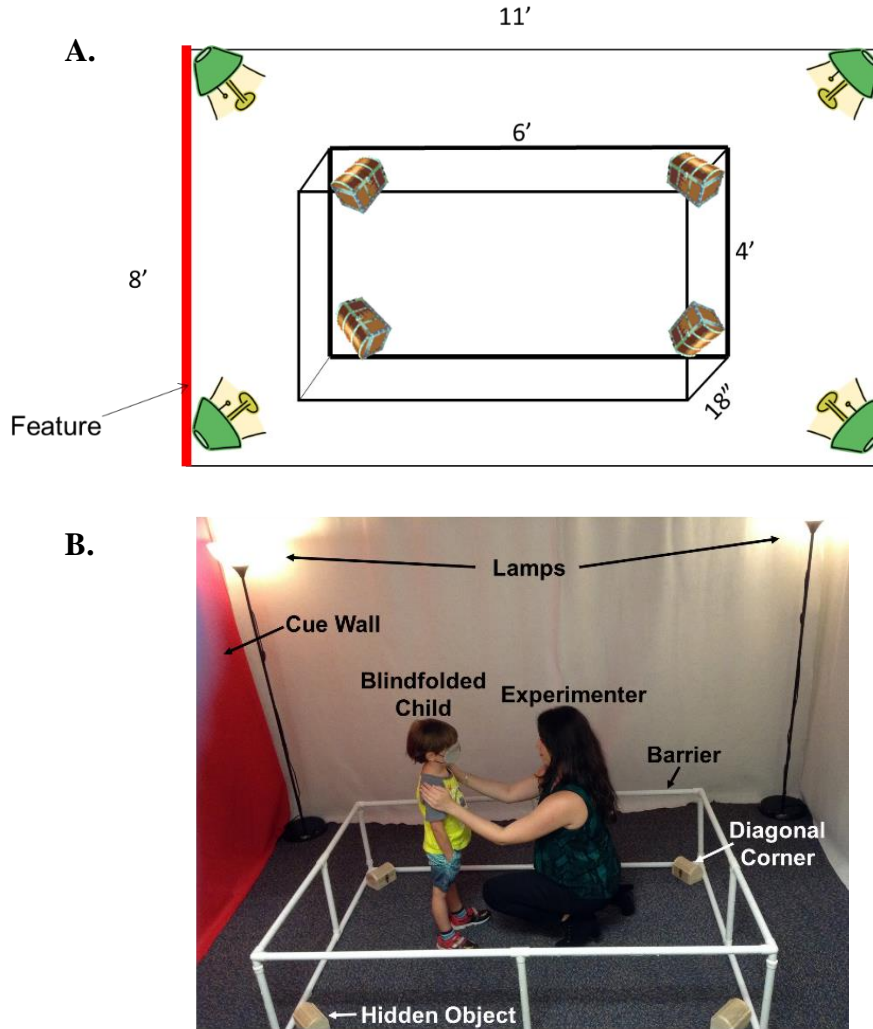


Figure 1. Panel A shows a diagram of the reorientation room setup with its features, objects, and dimensions. Panel B shows a child and an experimenter standing in the center of the 6'x 4' barrier with 1 treasure chest in each corner. The outer 11' by 8' enclosure was made up of three white walls (only 2 shown), one red (feature) wall, and a blue fabric that served as the ceiling of the room (not shown). One lamp sat in each of the 4 corners (only two shown).

For each child, I recorded the frequency with which they chose each corner (i.e., correct corner, diagonal corner, nearest to the correct corner, and farthest from the correct corner) and created a percentage score for each corner ($\# \text{ X corner chosen} / 8 \text{ trials} \times 100 = \% \text{ X corner chosen}$). Children's correct, diagonal, and near correct corner percentage scores reflected their use of different strategies for reorienting. For example, if children

predominantly chose the correct corner on the spatial reorientation test, then that suggests they used both geometric and landmark cues to solve the task (i.e., Combined Strategy Score = % correct corner). In contrast, if children typically chose either the correct or diagonal corners, then that suggests they solely used the geometric cues from the shape of the room to solve the task (i.e., Geometric Strategy Score = % correct corner + % diagonal corner). Lastly, if children usually chose the two corners closest to the salient, red wall, then that implies they relied on the landmark cue to solve the task (i.e., Landmark Strategy Score = % correct corner + % near correct corner). I examined each strategy score separately as a dependent measure.

Left-Right Assessment: For the specific language assessment, children were asked to raise their right and left hands eight times (RLLRLRRL format) to assess whether they understood the difference between right and left directions. This task took less than one minute to administer. Scores for each child were calculated based on both the number of times they raised the correct hand when asked eight times and the number of times they raised the correct hand when asked the first two times (both scores were converted to a percent for analyses). I decided to assess both scores as dependent measures since children may have known their left from their right hand on the first two trials but may have been confused by the demands of the task, having to raise their hands subsequently in a non-alternate order (i.e., RLLRLRRL instead of RLRLRLRL).

Boehm-3 Preschool Test of Basic Concepts (Boehm-3): For the general relational language assessment, the Boehm-3 (Boehm, 2001; See Figure 2 for sample item) was administered to assess children's understanding of basic spatial and relational concepts, including size (e.g., *tallest*), direction (e.g., *in front*), position in space (e.g., *nearest*),

time (e.g., *before*), quantity (e.g., *some, few, more*), and classification (e.g., *all*). In this task, children were shown pictures of various basic spatial and relational concepts and were asked to point to the correct answer (e.g., point to the dog that is *nearest* to the tree). All children were asked to complete 52 items, with each concept being tested twice to ensure that children understood the concept across more than one example. The Boehm-3 took children roughly 7-10 minutes to complete. Scores for each child were calculated based on the percent of items they answered correctly.

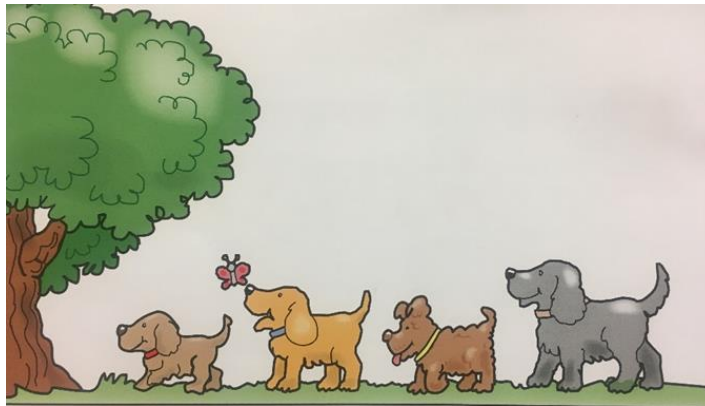


Figure 2. Sample item from the Boehm-3. Child was asked to point to the dog nearest to the tree.

Mental Rotation Test: As a small-scale spatial task, the Children's Mental Transformation Task (CMTT; Ehrlich, Levine, & Goldin-Meadow, 2006; see Figure 3 for sample item) was administered to evaluate children's ability to mentally rotate and translate two shapes to make a whole object. Children were shown two pieces of shapes and four target shapes on each trial and asked to point to the shape that the two pieces would make when put together. The CMTT consists of 32 items, including four types of items that tap into two-dimensional mental transformations: horizontal translation, diagonal translation, horizontal rotation, and diagonal rotation. Trials varied with respect

to which kind of two-dimensional (2D) mental transformations they required children to use. Children typically completed this assessment in 10-15 minutes. Each correct response received one point, resulting in a range of possible scores between 0 and 32. Raw scores were then converted to a percent of items answered correctly. This mental rotation test for children served as a spatial control task since I did not predict that success on this task would involve children's knowledge of spatial relational terms.

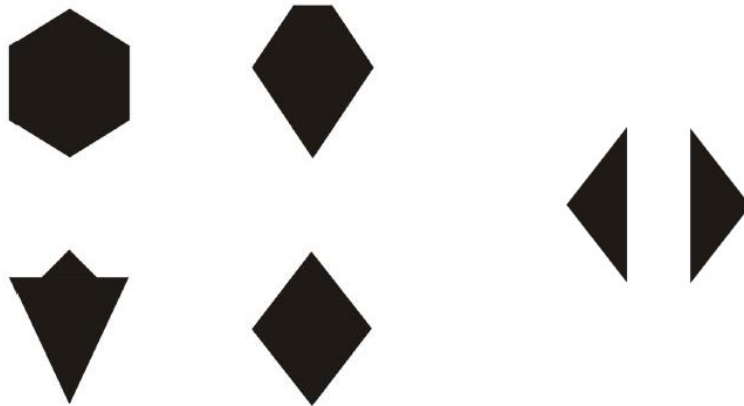


Figure 3. Sample item from CMTT. Child was asked to point to which one of the four shapes (left) the broken pieces (right) would make when put together.

Processing Speed Test: As a proxy for general intelligence, I administered the NIH Toolbox Pattern Comparison Processing Speed (PCPS) Test (Carlozzi, Beaumont, Tulskey, & Gershon, 2015; See Figure 4 for sample item), which is a standardized, computer-generated task that measures processing speed by asking children to decide whether two side-by-side pictures are the same or different. The entire test took approximately 5 minutes to administer. Data were collected and stored on an 11" iPad via the NIH Toolbox program application. Children's raw scores consisted of the number of items they answered correctly in a 90-second period. This test served as a non-spatial

control task, which I did not expect to be related to children's understanding of spatial relational language.

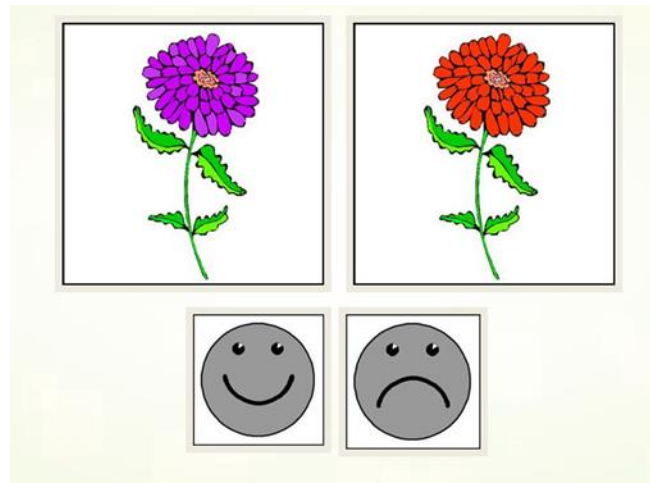


Figure 4. Sample PCPS item. Child was asked to click on the face denoting whether the items looked the same (corresponded with happy face) or different (corresponded with sad face).

RESULTS

Outliers, defined as data points that were located above or below 3 standard deviations from the mean, were assessed prior to data analyses. In total, seven outliers were identified: two from the Geometric Strategy Score, four from the left-right assessment, and one from the Boehm-3 test. Results are reported without outliers. There were no floor or ceiling effects since performance was variable across all tasks (see range of scores for all tasks in Table 3). Furthermore, independent samples t-tests revealed that there were no significant gender differences in any of the variables. Table 3 demonstrates the descriptive statistics for each variable, separated by participant sex assigned at birth. In addition, paired samples t-tests revealed that, overall, children chose the correct corner significantly more often than its geometrically equivalent, diagonal corner ($t [38] = 4.46$;

$p < 0.001$) on the spatial reorientation test. Figure 5 demonstrates the percentage of trials children chose the correct (C), diagonal (D), near correct (N), and far correct (F) corners.

Variable	<u>Girls</u>		<u>Boys</u>		<u>All</u>			
	<i>M(SD)</i>	<i>n</i>	<i>M(SD)</i>	<i>n</i>	<i>M(SD)</i>	<i>n</i>	Min	Max
Age at Visit	5.62 (0.86)	19	5.51 (0.89)	20	5.57 (0.86)	39	4.29	6.99
Combined Strategy (%)	4.74 (1.70)	19	4.70 (1.84)	20	4.72 (1.75)	39	2	8
Geometric Strategy (%)	7.47 (0.70)	19	7.00 (1.17)	20	7.23 (0.99)	39	6	8
Landmark Strategy (%)	5.05 (1.51)	19	5.2 (1.64)	20	5.13 (1.56)	39	2	8
Left-Right Assessment (all eight trials)	6.53 (2.39)	19	5.85 (2.37)	20	6.18 (2.37)	39	0	8
Boehm-3 Preschool Test of Basic Concepts (%)	47.84 (4.54)	19	47.75 (4.17)	20	47.79 (4.29)	39	35	52
Children's Mental Transformation Task (%)	16.95 (4.52)	19	19.30 (6.39)	20	18.15 (5.61)	39	6	30
Pattern Comparison Processing Speed Test	27.94 (7.46)	19	27.65 (7.37)	20	27.79 (7.31)	39	10	45

Table 3. Means and Standard Deviations of Variables by Participant Sex Assigned at Birth. Sex assigned at birth was dummy coded as 0 for girls and 1 for boys.

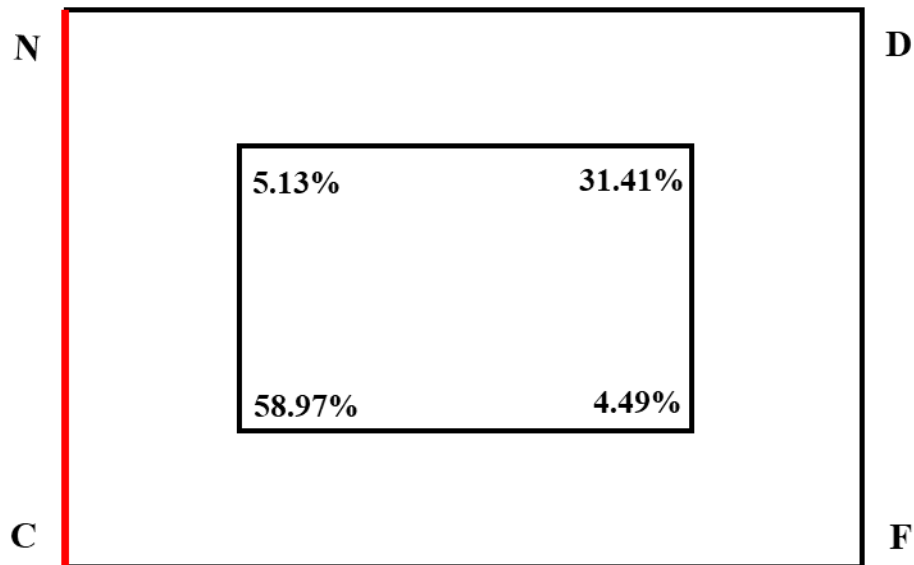


Figure 5. Percentages of responses to each corner over eight trials during the Spatial Reorientation Test. Corners are denoted by the letters C for correct corner, D for diagonal corner, N for the incorrect corner nearest to the correct corner, and F for the incorrect corner farthest from the correct corner.

Bivariate correlations revealed that children’s scores on all eight trials of the left-right assessment were significantly, positively correlated with their overall Boehm-3 test scores ($r=0.338$; $p=0.038$). Moreover, children’s scores on the first two trials of the left-right assessment were marginally, positively correlated with their overall Boehm-3 test scores ($r=0.339$; $p=0.050$). However, children’s knowledge of, specifically, spatial reorientation *task-relevant terms* on the Boehm-3 was significantly, positively correlated with their knowledge of left and right across all eight trials ($r=.451$; $p=.004$), the first four trials ($r=.487$; $p=.002$), and the last four trials ($r=.413$; $p=.009$). Table 4 demonstrates the bivariate correlations among age at visit, the spatial reorientation variables (i.e., Landmark, Geometric, and Combined Strategy Scores), left-right knowledge assessment, Boehm-3 test scores, CMTT scores, and PCPS test scores.

	1	2	3	4	5	6	7	8
1. Age	-							
2. Combined Strategy	.538***	-						
3. Geometric Strategy	.454*	.543**	-					
4. Landmark Strategy	.407*	.942***	.362*	-				
5. Left-Right Assessment	.323	.007	.471**	-.152	-			
6. Boehm-3 Scores	.605**	.348*	.248	.267	.339*	-		
7. CMTT Scores	.577***	.306	.197	.226	-.005	.305	-	
8. PCPS Scores	.716***	.459*	.325	.361*	.279	.578***	.454*	-

*Table 4. Pearson's Bivariate Correlations between Age at Visit, Combined Strategy Scores, Geometric Strategy Scores, Landmark Strategy Scores, Left-Right Assessment Scores, Boehm-3 Preschool Test of Basic Concepts Scores, Children's Mental Transformation Task (CMTT) Scores, and Pattern Comparison Processing Speed (PCPS) Scores. ***Denotes $p < 0.001$; **Denotes $p < 0.01$; *Denotes $p \leq 0.05$*

Next, I designated which words on the Boehm-3 test denoted spatial locations and directions (e.g., nearest, across, front) and which words I thought were most relevant to the spatial reorientation test (e.g., different, longest, tallest). Task-relevant, or task-based, terms are those that children might use to solve, specifically, the spatial reorientation test. Each term on the Boehm-3 assessment was asked about twice in different contexts. Table 5 provides a list of all terms found on the Boehm-3 test that fall into the categories of spatial location/direction and spatial reorientation task-relevant words. Several words overlapped across both categories (i.e., nearest, across, in front, farthest, between) and, thus, appear twice in the table. I found that children's understanding of task-relevant words on the Boehm-3 was significantly, positively correlated with their understanding of left and right across all eight trials ($r=0.442$; $p=0.005$), the first two trials ($r=0.412$;

$p=0.016$), the first four trials ($r=0.483$; $p=0.002$), and the last four trials ($r=0.401$; $p=0.013$). Then, in line with my specific aims, I analyzed the relations between children’s use of spatial reorientation strategies and their knowledge of left and right directions as well as general and specific relational words.

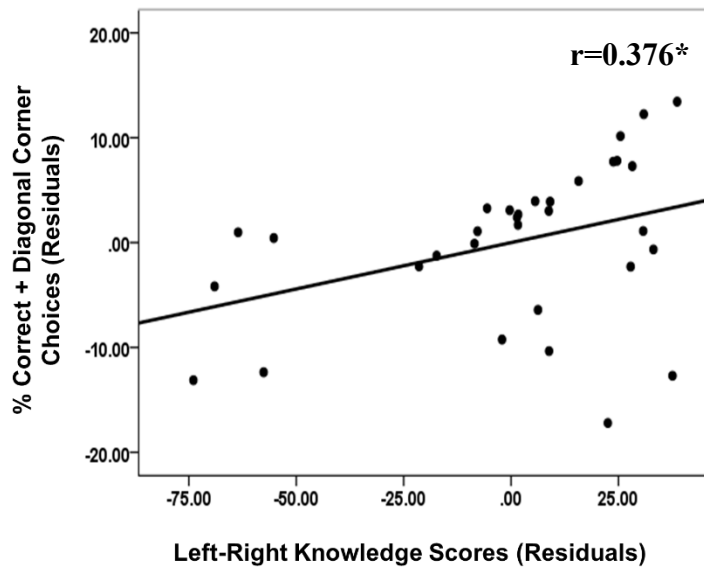
Spatial Locational and Directional Terms	Spatial Reorientation Task-Relevant Terms
Nearest	Nearest
Across	Across
In Front	In Front
Around	Different
Before	Longest
Farthest	Farthest
Lowest	Tallest
Last	Same
Bottom	Largest
Middle	Shortest
First	First
Between	Between

Table 5. List of Boehm-3 terms that denote spatial locations/directions and terms that may be useful for solving the spatial reorientation test.

Aim one explored whether children’s understanding of left and right directions was related to their performance on the spatial reorientation test. Bivariate correlations revealed that children’s scores on all eight trials ($r=0.365$; $p=0.026$) as well as the first two trials ($r=0.471$; $p=0.006$) of the left-right assessment were significantly, positively correlated with their correct plus diagonal corner choices (i.e., Geometric Strategy Scores) on the spatial reorientation test. Furthermore, multiple regression analyses

showed that when controlling for age, CMTT scores, and PCPS test scores, children's scores on the first two trials of the left-right assessment were significantly, positively associated with their Geometric Strategy Scores (see Figure 6A; $B=0.088$; $p=0.044$) but not their Landmark Strategy Scores (i.e., near plus correct corner choices; $B=-0.190$; $p=0.062$) or Combined Strategy Scores (i.e., correct corner choices; $B=-0.125$; $p=0.252$). In addition, with all else equal, children's overall scores on the left-right assessment (i.e., 8 trials) were marginally, positively related to their Geometric Strategy Scores ($B=0.101$; $p=0.050$).

A. Directional Language Predicted Geometry Use on a Spatial Reorientation Test



B. General Relational Language Did Not Predict Geometry Use on a Spatial Reorientation Test

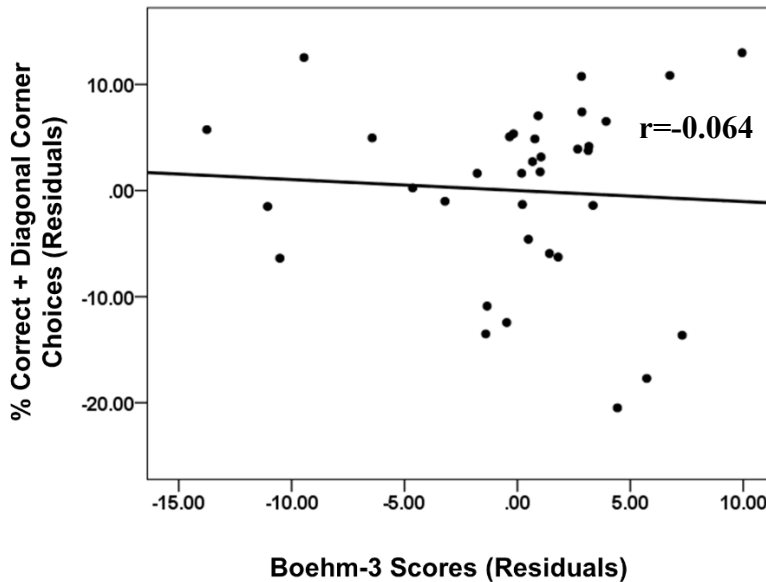


Figure 6. Partial regression plots of individual differences in associations between geometry use on a spatial reorientation task and comprehension of (A) left and right directions and (B) generic relational concepts. Children with higher scores on the first two trials of the left-right assessment (A), but not higher scores on the Boehm-3 (B), gravitated more often toward the correct and diagonal corners on the Spatial Reorientation Test, independent of age. *Denotes $p < 0.05$.

Next, to examine whether specific rather than general spatial language related to individual differences in spatial reorientation strategies, I added general spatial language (i.e., overall Boehm scores) as a covariate in the multiple regression analyses. I found that when I controlled for age and scores on the CMTT, PCPS test, and Boehm-3 test, children's left-right assessment scores on all trials ($B=0.108$; $p=0.045$) and the first four trials ($B=0.109$; $p=0.043$) significantly, positively predicted only their Geometric Strategy Scores on the spatial reorientation test.

Aim two investigated whether children's knowledge of basic relational terms (e.g., near, around, in front) was associated with their spatial reorientation strategies.

Children's scores on the Boehm-3 test were significantly, positively correlated with their correct corner choices (i.e., Combined Strategy Scores; $r=0.348$; $p=0.032$) and inversely correlated with their diagonal corner (i.e., geometrically equivalent but incorrect corner) choices ($r=-0.369$; $p=0.023$) on the spatial reorientation test. Multiple regression analyses, however, revealed that when controlling for age, CMTT scores, and PCPS test scores, children's Boehm-3 test scores did not relate to their correct responses (i.e., Combined Strategy Scores; $B=0.104$; $p=0.859$) nor their Geometric Strategy Scores (See Figure 6B; $B=-0.104$; $p=0.729$) on the spatial reorientation test.

Next, I examined the relations between comprehension of specific Boehm words denoting spatial locations and directions and performance on the spatial reorientation test. I conducted Pearson's correlations and found that children's knowledge of spatial locational and directional terms on the Boehm-3 was significantly, positively correlated with their Combined Strategy Scores ($r=0.342$; $p=0.033$) and Landmark Strategy Scores ($r=0.318$; $p=0.048$) on the spatial reorientation test. The same results held whether I included or excluded outliers. However, further multiple regression analyses revealed that understanding these specific kinds of spatial terms did not predict children's use of geometric ($B=65.76$; $p=0.107$), landmark ($B=87.65$; $p=0.223$), or combined ($B=103.05$; $p=0.164$) strategies on the spatial reorientation test when controlling for age as well as scores on the Boehm-3, CMT, and PCPS tests.

DISCUSSION

Because language shapes the way we think and talk about the world, I sought to measure early understanding of words that describe space and the relations between oneself and objects in space to investigate whether children's comprehension of spatial

language relates to their spatial reorientation performance. Specifically, I asked whether comprehension of specific spatial words or many different types of spatial words would be associated with individual differences in children's use of different strategies to solve a spatial reorientation test. Aim one explored children's knowledge of directional words (e.g., left, right) in relation to their spatial reorientation strategies via their corner choices. Aim two explored children's knowledge of basic relational words (e.g., near, around, in front) in relation to their spatial reorientation strategies. The current study differs from other studies on spatial language in that I tested both children's knowledge of specific, task-relevant, and locational/directional terms as well as their comprehension of basic but generic relational concepts. Furthermore, I examined whether these two kinds of spatial language tests (i.e., specific and general) were associated with a large- (i.e., spatial reorientation) scale spatial task while controlling for age as well as performance on a small-scale (i.e., mental rotation) spatial task and a non-spatial task (i.e., processing speed).

In accordance with aim 1, I found that when controlling for age, mental rotation, processing speed, and comprehension of general relational concepts, children who knew right from left were better able to encode the geometry (i.e., shape) of the room (but not combine geometry with the landmark wall) when solving the spatial reorientation task. In line with aim 2, I found that children's understanding of relational terms, as measured by the Boehm-3, was positively associated with their ability to successfully reorient to goal locations on a spatial reorientation test. Furthermore, children's correct responses on the spatial reorientation test were positively associated with their comprehension of spatial locational and directional Boehm terms (e.g., nearest, across, last, lowest), but not when

controlling for age and performance on the control tasks. Therefore, with all else constant, children's performance on the Boehm-3 did not predict their use of the most successful reorientation strategy (i.e., a combined strategy). In addition, children's knowledge of left and right directions was positively associated with their comprehension of spatial reorientation task-relevant words on the Boehm-3. This is not surprising given that it has been proposed that understanding directional terms like left and right may help children solve spatial reorientation tests involving landmarks (Shusterman & Spelke, 2005). The current study's findings suggest that while knowledge of relational concepts grows with age along with spatial reorientation abilities, individual differences in children's understanding of specific spatial concepts (i.e., left and right), as opposed to relational language more broadly, may help them use the geometric properties of space to narrow down their choices when searching for target locations after being disoriented.

Thus far, much of the research on the effects of language on spatial reorientation and navigation abilities has focused on how a sense of left and right or comprehension of other spatial locative terms (i.e., below, in, near) can aid in either reorienting or navigating by landmarks (Nardini, Atkinson, & Burgess, 2008; Piccardi et al., 2015). Findings have shown that the acquisition of left and right, for example, correlates with successful use of landmarks on spatial reorientation tests (Hermer & Spelke, 1996; Pyers et al., 2010). However, ideas as to whether language is *necessary* for successful reorientation using landmarks (Newcombe & Ratliffe, 2007; Bek, Blades, Siegal, & Varley, 2010), and whether the development of spatial language is the reason children switch from reorienting solely by geometry to doing so by combining geometry with landmarks (Learmonth, Newcombe, Sheridan, & Jones, 2008) continue to be challenged.

Interestingly, the current study did not find a relation between children's correct sense of left and right and successful reorientation performance. Rather, I found that independent of age, children's knowledge of left and right was positively related to their use of geometry on the spatial reorientation test. While this may seem peculiar, it makes sense given that the correct corner and its geometrically equivalent corner are both to the same side of the child when the child is facing each short wall. Thus, if during a standard spatial reorientation task, a child is facing the short wall closest to the correct corner on their left, and the child understands this spatial relation, then they may believe the diametrically opposed corner *is* the correct corner since it is also to their left when facing its respective wall. Hence, it is possible for children to ignore the landmark wall while still implementing their sense of left and right to try and solve the task, even if sometimes unsuccessfully.

The current study is not without its limitations. For one, it is correlational, not experimental, so I caution against making any causal claims based on these findings. Future studies may want to design experimental manipulations such as training a group of young children to learn left versus right or other task-relevant words and subsequently comparing their spatial reorientation performance to another age-matched group of children who are not familiar with such language. With further investigation, we may be able to disentangle the causal relation between language and spatial cognition. For instance, does knowing spatial language help us understand and, thus, navigate the spatial world more accurately and effectively (in line with the Whorfian-hypothesis; Hunt & Agnoli, 1991) or do our preformed cognitive representations of space elicit spatial language use to help us make sense of the environment whenever we navigate it

(consistent with the anti-Whorfian-hypothesis; Casasanto, 2008)? As Hayward and Tarr (1995) point out, visual representations of space may be organized according to the spatial terms already developed to describe spatial relations or, in turn, the structure of spatial language may be formed depending on pre-existing encoding of spatial representations. Nevertheless, it is possible that the relation is bidirectional: toddlers, for instance, can still cognitively encode and represent the world around them without much, if any, linguistic resources (Learmonth, Newcombe, & Huttenlocher, 2001), but as they develop language, they may come to rely on it to solve novel spatial tasks more efficiently than they would without the aid of language. Secondly, the spatial tasks (i.e., spatial reorientation, mental rotation) I use in the current study are constructed and artificial; thus, a more naturalistic study design may better help us learn about the impact of language on spatial abilities in the real world.

Furthermore, while some studies on the development of the relation between language and spatial abilities test children's *production* of spatial words (e.g., Pruden et al., 2011), the current study uses the Boehm-3 Preschool Test of Basic Concepts, a pointing task that helps us gauge 3-5-year-old children's grasp of relational—not necessarily spatial—concepts. However, the Boehm-3 may not be the best test of spatial language comprehension, and it does not evaluate language production skills at all. Thus, since comprehension of concepts usually precedes the expression of those ideas, more spatial and language researchers may want to consider using a combination of language comprehension and production tests (e.g., Dessalegn & Landau, 2008) as well as other means of assessing language comprehension skills in young children, such as eye-tracking to examine where children look when asked about spatial concepts (e.g., look

at/find the girl *on top* of the chair). In this manner, we can get a more comprehensive look at how young children's understanding *and* active use of language facilitate their spatial abilities.

Overall, this study may offer insights into the associations between understanding relative frames of reference and the strategies young children use to find their bearings, suggesting that psychological constructs like language may influence spatial cognition in early childhood. Thus, parents and teachers may want to engage in talk about basic directions with children at earlier ages, teaching them the difference between left and right in preschool rather than, more commonly, in early elementary school. Furthermore, the language children hear from their caregivers when participating in spatial activities (e.g., sports, games, toys) can have positive effects on language production and spatial achievements (Pruden, Levine, & Huttenlocher, 2011). Thus, including spatial language among other known predictors of spatial reasoning (e.g., hippocampal growth and volume, spatial experience) can offer us a richer understanding of the development of human spatial cognition.

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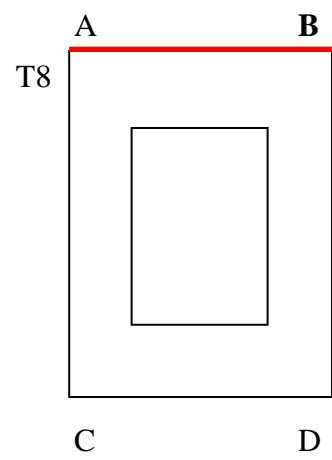
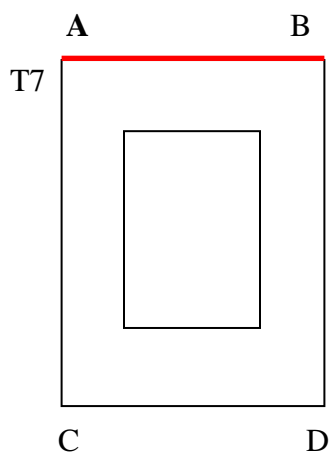
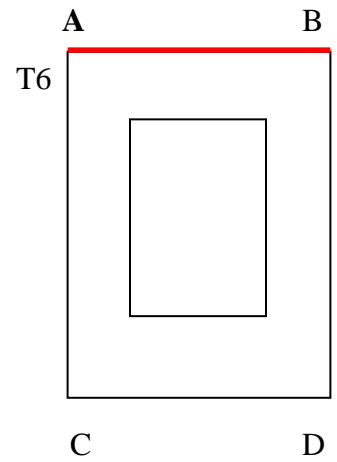
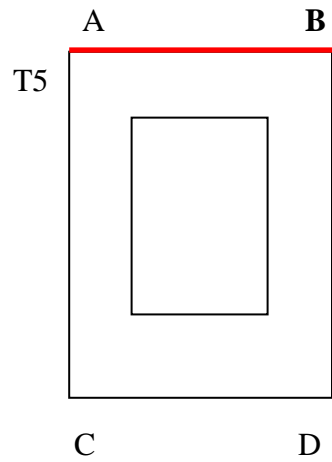
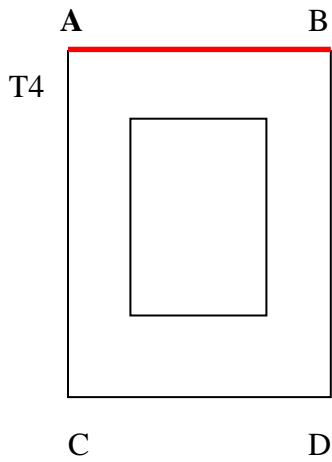
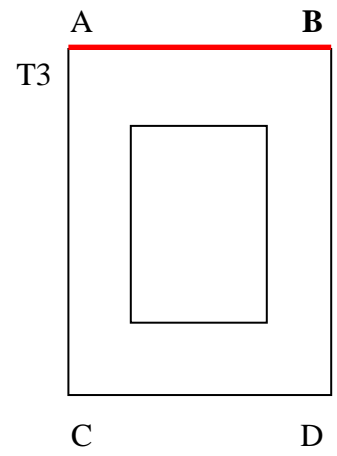
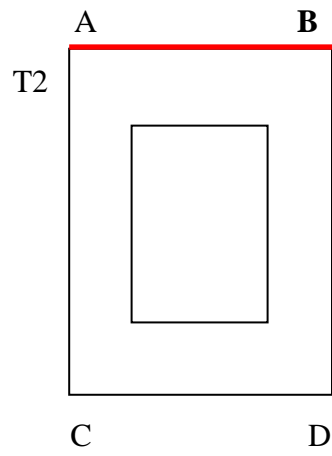
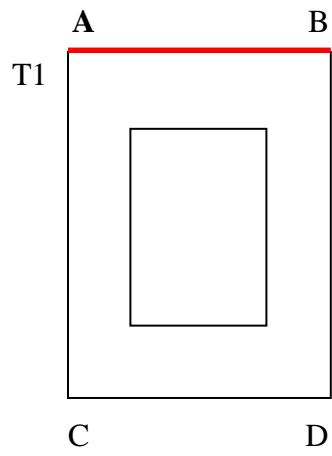
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Appendix 1 – Scoring Sheets for Spatial Reorientation Test and Left-Right Assessment

Date: _____

Participant ID #: _____



Date: _____

Participant ID #: _____

Instructions: Ask child: "Please raise your **right/left** hand." (After child complies):
"Please put your hand down." Alternate between right and left for 8 trials as shown
below. In each box, place a check mark or X if they got the correct or wrong answer,
respectively

****Have child turn around so that their back is to you (their right and left hand will
match yours).****

Right/Left	R	L	L	R	L	R	R	L
Correct?								

VITA

VANESSA VIEITES

- 2012 B.A., Psychology
Smith College
Northampton, MA
- 2017 M.S., Psychology
Florida International University
Miami, FL
- 2017 -2021 Doctoral Candidate
Psychology
Florida International University
Miami, FL

SELECT PUBLICATIONS & PRESENTATIONS

1. Vieites, V., Pruden, S. M., & Reeb-Sutherland, B. C. (2020). Childhood wayfinding experience explains sex and individual differences in adult wayfinding strategy and anxiety. *Cognitive Research: Principles and Implications*, 5(1), 1-16.
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