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An Analysis of Bilateral Tripart Hippocampal Volume and its Relation to Spatial Processing in a Middle Childhood Sample

Emily Marler
marler8@siu.edu

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Emily Marler
Advisor: Dr. Michelle Kibby
Department of Psychology, Southern Illinois University Carbondale
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Abstract

Throughout the years, animal research has unearthed that certain cells in the hippocampus contribute to spatial processing, which involves an animal's recognition of its environmental layout and directionality. In order to apply this work to human children, we will identify whether hippocampal volume is related to spatial processing, including identifying which section(s) of the hippocampus seem to be more related to processing layouts versus directionality. Based on previous literature (Goodrich-Hunsaker, Hunsaker, & Kenser, 2005; McHugh, Fillenz, Lowry, Rawlins, & Bannerman, 2010), we predicted there would be a relationship between bilateral posterior and middle hippocampal regions and spatial processing, such that decreased hippocampal volume of these areas would correspond with worse spatial processing. This project includes structural magnetic resonance images (MRI) from 136 children (8-12 years old) with the neurodevelopmental disorders of Attention-Deficit/Hyperactivity Disorder (ADHD), Reading Disability (RD) and comorbid ADHD/RD, as well as typically developing controls. Analyze software was used for tracing the hippocampus on these images and for segmenting bilateral hippocampal volume into three sub regions (anterior, middle, and posterior). Spatial processing was assessed with WISC Block Design, Development Test of Visual Motor Integration (DTVMI), NEPSY Visual Attention, and NEPSY Design Fluency. Linear regressions indicated that bilateral anterior, middle, and posterior hippocampal volume were significant predictors of all measures of spatial processing except Block Design. Our results provide evidence that all regions of the hippocampus are associated with spatial processing.

An Analysis of Bilateral Tripart Hippocampal Volume and its Effects on Spatial Processing in a Middle Childhood Sample

The hippocampus is a gray matter structure of serious consideration due to its wide array of functions, including memory (both spatial and non-spatial), learning, and emotion (Bisby, Horner, Hørlyck, & Burgess, 2016). However, most studies focusing on the hippocampus utilize functional magnetic resonance imaging (fMRI) or event-related potentials (ERP) to determine which kinds of tasks activate the hippocampus. Consequently, only a small amount of research focuses on structural MRI scans, which allow scientists to determine the size of brain structures (Symms, Jäger**,** Schmierer**,** & Yousry, 2004). Even though structural MRI scans are not commonly utilized in research, they are still important: Researchers can determine psychopathology and pathology by comparing volumes of certain brain structures in unhealthy individuals to the volumes in healthy individuals (Symms et al., 2004). For instance, hippocampal sclerosis, severe neuron cell loss in the hippocampus, is diagnosed by comparing hippocampal volume in patients with epilepsy and control participants (Symms et al., 2004). The current study utilized structural MRI scans to show that hippocampal volume of the posterior and middle regions have an impact on an individual's spatial processing ability.

What is Gray Matter and How Does it Develop?

The brain is composed of 60% white matter and 40% gray matter (Roberts, Anderson, & Husain, 2017). White matter is comprised of myelinated axons, which allow electrical impulses to travel at tremendous speeds (Roberts et al., 2011). Gray matter consists of neuron cell bodies and dendrites, which have several functions: muscle control, sensory registration and perception (including seeing or hearing), memory, emotion, speech, decision-making, and self-regulation

(Dalwani et al., 2015). For the purposes of this study, we only focused on gray matter properties since we studied cognitions that are theorized to be largely conducted by gray matter.

Gray matter growth and development occurs quite rapidly during childhood. By the age of six, roughly 95% of the brain has been physically developed, including the pruning of excess synaptic connections (Spear, 2013). Synaptic connection pruning refers to the cutting away or removal of superfluous neurons that are not being employed or utilized during brain processes, which occurs around the ages of two to three (Spear, 2013). During adolescence, a second pruning period occurs that removes even more synapses that have not been used or strengthened over the years. If the mind is not cognitively challenged throughout adolescence, certain synapses will dissipate (i.e., less connections that allow for quick and easy neuronal firing). In contrast, synaptic connections strengthened by cognitive stimulation will result in the growth and facilitation of neuronal communication. For example, in early childhood, children are unable to differentiate their native language from other languages. However, as children are repeatedly exposed to their native language, including communication with family members or others, their brain circuits for language strengthen to respond to their native language over others (Graham, 2011). This phenomenon is often called “use it or lose it”, referring to the idea that if certain pathways in the brain are not used during early childhood and again in adolescence, the ability to complete certain actions or thought processes associated with those neurons will be lost. Though the loss of synaptic connections seems harmful, it is actually beneficial: synaptic connections expend energy, so reductions allow the brain to become more efficient and closely resemble typical adult brains, in which higher forms of thinking and informational processing are observed (Spear, 2013). While synaptic pruning is a natural developmental process in children and

adolescents and involves the loss of neurons that are not frequently accessed, overall gray matter volume can have certain consequences on an individual's outward behavior.

Brain Volume Effects on Behavioral Function

Previous literature demonstrates relationships between an individual's behavioral function and the volume of a brain structure. For instance, individuals with reduced total gray matter volume have worse memory than those whose total gray matter volume is not reduced (Mummery et al., 2000). However, excess total gray matter volume is related to high levels of distractibility in children and adults (Kanai, Yuan Dong, Bahrami, & Rees, 2011). Regardless of functionality, cortically thicker brains are typically healthier, since fat tissue is used to insulate neurons to allow messages to rapidly travel through the brain (Roberts et al., 2011). Undeniably, the amount of gray matter does not always correlate with function; there are instances when it would appear advantageous to have increased amounts (Mummery et al., 2000), but also cases where it is better to have reduced amounts (Kanai et al., 2011). Researchers are not aware of the implications of more or less gray matter until they directly recognize how the observed behavior is related to brain volume.

Hippocampus Structure and Function

The hippocampus, which is a small gray and white matter structure in the temporal lobe, is implicated in learning and memory (Koch, Reess, Rus, & Zimmer, 2016), and is also a part of the limbic system, which is associated with emotional reactivity and regulation (Watson & Breedlove, 2016). Commensurately, the hippocampus is activated during memory tasks that involve emotionality (Bisby et al., 2015). Bisby and coworkers' (2015) study involved showing participants a series of images with an equal distribution of positive, negative, and neutral images from the International Affective Picture Set (Lang, Bradley, & Cuthbert, 1999). Participants

exhibited decreased hippocampal activity when presented with images that elicited negative emotions, such as abused dogs (Bisby et al., 2015). Additionally, emotional support from mothers in early childhood results in increased hippocampal volume during early adolescence and onward (Luby, Belden, Harms, Tillman, & Barch, 2016). Learning is also associated with hippocampal volume: the more information learned and stored in memory, the greater the hippocampal volume (Koch et al., 2016). Another function related to the hippocampus is verbal memory, such that increased left hippocampal volume is associated with higher verbal memory performance (Hoseth et al., 2016). Spatial processing, the ability to detect locations of objects in space (Tsanov & O'Mara, 2015), spatial reasoning, and spatial memory, the memory for spatial information (Bird & Burgess, 2008), are also hippocampal functions, all of which were the focus of the current study. Four types of cells allow the hippocampus to be involved with memory, learning, emotion, spatial processing, spatial reasoning, and spatial memory: place cells, grid cells, head direction cells, and boundary cells (Bird & Burgess, 2008; Hafting, Fyhn, Molden, Moser, & Moser, 2005; Taube, Muller, & Ranck, 1990; Hartley et al., 2014).

Place, Grid, Head Direction, and Boundary Cells

Limited research has been conducted on the four hippocampal cells in humans. However, the hippocampal cells in humans function quite similarly to hippocampal cells in rodents (Wolbers, Weiner, Hanspeter, Mallot, & Büchel, 2007). Therefore, the current study utilized animal research to describe these different cells. Place cells and grid cells allow rodents to detect location in space (Bird & Burgess, 2008). Place cells fire at all times when the animal is within an environment (referred to as the 'place field'), allowing animals to construct a mental representation of their surroundings (Russell, Horii, Smith, Darlington, & Bilkey, 2003) and code for locations of both objects and body parts in space (Lenck-Santini, Muller, Save, &

Poucet, 2002). The vestibular system, which contributes to proprioception (i.e., the ability to know the position of the limbs without looking at the body), combined with external cues in the environment, serve to assist place cells by solidifying the animal's location based on its movement (Whishaw, 1998). If an animal is in a once familiar environment that has been altered, then place field firing will change to indicate that the animal is in a novel environment. Place cells fire at low rates continuously throughout the animal's lifetime, but increase when an animal is in a particular region in their natural, familiar environment in which they typically reside (Hartley, Lever, Burgess, & O'Keefe, 2014). Grid cells also fire in specific locations in the environment similar to place cells, but they do so in a triangular pattern, known as the "grid" (Hafting et al., 2005). The three parameters used to describe the triangular grid are spacing, orientation, and spatial phase (Hafting et al., 2005). Spacing refers to the distance between grid fields, orientation refers to the tilt of the specified grid compared to the reference point, and the spatial phase is the displacement of differing directions relative to a reference point (Moser & Moser, 2007). The triangular grid field involves three equal sections invariant of change in an animal's speed, direction, and movement (Hafting et al., 2005). This coordinated space grid cells create is activated at all times in a human or rodent's environment regardless of landmark cues, which suggests that grid cells are receiving information from other stimuli not associated with the external environment (Moser & Moser, 2007). Additionally, when the hippocampus is momentarily inactivated, grid cell firing drastically decreases, hinting at an association between grid cell firing and hippocampus activation (Bonnevie et al., 2013). Place and grid cells are essential for determining environmental location, and firing rates change based upon the type of environment a human or rodent is in (such as increased firing for new locations). Since the function of place and grid cells in rodents are quite similar to place and grid cells in humans

(Wolbers et al., 2007), the current study assumed that the aforementioned mechanism for operation is the same.

Along with place and grid cells, head-direction cells and boundary cells are also found in the hippocampus of rodents and humans (Wolbers et al., 2007). Head-direction (HD) cells serve as an internal compass: these cells point the animal in the appropriate direction by firing rapidly when facing that appropriate direction and firing at low intervals when not (Taube et al., 1990). Unlike place cells, HD cells fire independently of the body's location in the environment; instead, HD cells respond to orientation and directionality (Taube et al., 1990). Boundary cells, as the name implies, fire when an animal is presented with an environmental boundary, such as a wall or other obstruction of movement at some distance and direction from the animal (Hartley et al., 2014). All these cells work together within the hippocampal formation to provide humans and rodents with the spatial navigation skills needed to function in the environment.

Path Integration

Place cells code for path integration, which refers to rodent spatial processing ability (Wolbers et al., 2007). Since animal studies are commonly used to test path integration, little is currently understood about the type of spatial processing humans possess. Wolbers et al. (2007) used fMRI to test humans during a virtual reality task in order to determine if path integration involves the same mechanisms found in rodents. Participants were instructed to move around two legs of a triangle before turning and indicating the starting point. Examination of fMRI results indicated stronger activation in the right hippocampus as opposed to the left during correct trials, which is in accordance with prior studies involving rodents (Jones & Wilson, 2005). From past work on path integration in rats (Wishaw, 1998), Wolbers et al. (2007) accurately determined that the cortical systems operate quite similarly. Even though spatial

processing studies have mainly focused on animal models, humans are closely related in terms of hippocampal functionality (Wolbers et al., 2007). Furthermore, since the hippocampus is implicated in path integration, it is intuitive to think that reduced hippocampal volume could potentially lead to path integration deficits, and therefore diminished spatial processing ability.

Spatial Processing: A Hippocampus Function

Spatial processing is the ability to detect objects in space, including extremities and object location, and it can be studied in both humans and rodents (Tsanov & O'Mara, 2015). Spatial processing skills allow humans and rodents to not only distinguish objects, but also locate objects (Mazzocco, Bhatia, & Lesniak-Karpiak, 2006). Children need spatial processing skills to calculate math operations, read, navigate the environment, and play sports or engage in physical activities (Brotons-Mas, O'Mara, & Sanchez-Vives, 2006). The association between mathematical ability and spatial processing most likely relates to the creation of a mental number line and being able to correctly align numbers in calculations, such as carrying and borrowing (Mazzocco et al., 2006). During middle childhood, schools begin teaching more complex mathematical problems that are more spatially demanding, which makes the development of spatial processing so important in this regard (Mazzocco et al., 2006). Reading also relies on spatial processing: individuals must be able to follow lines containing sentences correctly and accurately in order to comprehend the content (Mazzocco et al., 2006). While children in middle childhood have already been taught to read, reading skills are still developing due to the increasing complexity of the assigned literature (Hempenstall, 2010). Playing sports also requires spatial processing skills (i.e., being able to locate objects), such as catching a ball or staying inside the lanes on a track (Habacha, Mounaro, & Dosseville, 2014). Sports teams/clubs require athletes to practice skills because spatial processing improves with prolonged exposure (Habacha

et al., 2014). Spatial processing skills are utilized in everyday life by allowing individuals to interact with objects in the environment and function normally during routine tasks such as reading or solving a mathematical operation, which is crucial for healthy functioning.

Spatial Reasoning: A Hippocampus Function

Another function of the hippocampus is spatial reasoning, which enables individuals to find restaurants, stores, or houses without ever having been to the exact location due to the formation of cognitive maps, which are mental representations of an individual's environment (O'Keefe & Nadel, 1978). Cognitive maps and spatial reasoning allow humans to infer the basic layout of the environment without physically being present. Development of spatial reasoning is entirely natural: children learn by freely exploring the environment, using muscles and touch receptors as guides (Oudgenoeg-Paz, Leseman, & Volman, 2015). Babies learn to manipulate objects as they become mobile and learn about distances and sizes when they are able to move towards objects (Oudgenoeg-Paz et al., 2015). Certain situations can interfere with or prevent maturation of spatial reasoning, including developmental delay (e.g., a motor disorder such as cerebral palsy), lack of opportunity for the child to freely explore the environment during early developmental stages, or illness during key developmental periods (Eckersley, 2012). Indeed, such developmental obstacles can cause the pruning of synaptic connections in gray matter, particularly in the hippocampus; as a result, the potential to develop spatial reasoning skills is lost (Spear, 2013).

Spatial Memory: A Hippocampus Function

In order to understand how the hippocampus is involved in the memory for spatial information (spatial memory), two opposing theories have been described: the relational theory and the cognitive map theory (Bird & Burgess, 2008). The cognitive map theory posits that the

hippocampus is responsible for allowing animals and humans to explicitly create spatial representations of the environment in their minds (O'Keefe & Nadel, 1978). Conversely, the relational theory suggests that the hippocampus allows animals and humans to be primed to view certain stimuli as implicitly associated with one another (Cohen & Eichenbaum, 1993; Eichenbaum, 2004). According to the relational theory, the hippocampus primes certain environmental features in the brain, which allows the linkage between objects in the animal's surroundings. Kumaran and Maguire (2005) conducted a qualitative fMRI experiment to determine which theory is the more accurate when defining the function of the hippocampus as it relates to spatial memory. During the fMRI procedure, participants were presented with two separate tasks, ones that either followed the relational theory or the cognitive mapping theory. For the relational theory task, participants were to virtually give a crate of wine to a person they knew based on two constraints: if the person lived physically closer (spatial memory) or if the participant was friends with the person (social memory). In the cognitive map design, participants were asked to create mental images of where a friend lived (spatial memory) or to mentally imagine their friend's face (social memory). Kumaran and Maguire (2005) found that the hippocampus is functionally engaged during the tasks using imagery to determine where a friend lives or deciding which friend lives closer, which operates in alignment to O'Keefe and Nadel's (1978) cognitive map theory for spatial memory. Based on Kumaran and Maguire's (2005) research, the current study assumed that the hippocampus is better understood through the cognitive map theory, since it was activated during tasks designed to induce spatial memory.

In addition to hippocampal involvement with cognitive mapping, spatial processing, spatial reasoning, and path integration, the hippocampus is functionally activated when retrieving memories that contain spatial information. During a memory recall task in an fMRI procedure,

participants were asked to remember their spatial location when a particular event occurred (Hoscheidt, Nadel, Payne, & Ryan, 2010). Specifically, participants were asked to describe 30 common life events they were able to recall in great detail. Afterward, participants were either asked questions to elicit spatial or nonspatial information, including item of clothing worn at the time of the event (nonspatial information) and the location of the event (spatial information). The posterior region of the hippocampus exhibited stronger activation during retrieval of spatial memory, whereas the anterior region showed stronger activation during the retrieval of nonspatial memory (Hoscheidt et al., 2010). Additionally, during recall of familiar landmarks in another fMRI study, the posterior hippocampus was activated, whereas a bilateral parietal and frontal system was activated during recall of unfamiliar landmarks (Goel, Makale, & Grafman, 2004). Consequently, it is suggested that the posterior hippocampus is more involved with spatial memory and cognitive mapping than the anterior hippocampus since the familiar locations were better mentally represented in the individual's mind. Based on research by Hoscheidt et al. (2010) and Goel et al. (2004), it is suggested that the hippocampus is involved not only during tasks of spatial processing (O'Keefe & Nadel, 1978), but also in the simple recall of past experiences that involve spatial memory.

Sex Differences between Spatial Memory and Activation of the Hippocampus

Furthermore, there are sex differences in spatial memory and hippocampal activation, as indicated by an fMRI study (Sneider, Rogowska, Sava, & Yurgelun-Tod, 2011). Healthy human adults were given a virtual Morris water maze task, in which participants viewed a pool in the middle of a room. Four pictures were placed around the walls surrounding the pool, indicating north, south, east, and west, and participants were tasked to find the hidden platform in the pool by using the pictures as environmental cues. The right hippocampus was more strongly activated

in women, compared to the increased activation in the left hippocampus in men (Sneider et al., 2011). While the current study was not concerned with various sex differences during tasks of spatial processing, it is important to note they do exist and that the hippocampus is activated during such tasks. Hence, gender effects were assessed to determine whether gender should be used as a covariate. Additionally, the hippocampus is bilaterally larger in women compared to men (Cosgrove, Mazure, & Staley, 2007). Perhaps this larger volume corresponds to the increased activation women exhibit in the right hippocampus compared to men, suggesting that larger hippocampal volume leads to increased activation during spatial navigation/processing tasks.

Spatial Processing Deficits

Impairments in spatial processing have been investigated mainly through ethanol (the active ingredient in alcohol) administration to rodents (Matthews, Best, White, Vandergriff, & Simson, 1996). The hippocampus contains many receptors for the neurotransmitter glutamate and the presence of ethanol blocks glutamate receptors (glutamate antagonist), which interferes with hippocampal function (Matthews et al., 1996). As a result, ethanol significantly reduced the specificity of place cell firing of every recorded place cell in an awake rat. Once ethanol is no longer in the rat's system, place cell firing returns to normal and spatial processing is once again at baseline. Since ethanol is known to impair brain function, rats were injected with saline in the control group and differing levels of ethanol in the experimental groups and were evaluated during the Morris water maze task (Matthews et al., 1996). Rats that received higher doses of ethanol were significantly slower in locating the platform during the Morris water maze task than rats receiving lower doses, thus suggesting an association between the amount of ethanol consumed/injected and spatial processing ability. Therefore, once the hippocampus has been

compromised by ethanol, spatial processing ability diminishes. Humans are also impaired by ethanol (alcohol), with symptoms including ataxia (the inability to walk in a straight line), memory loss, and disorientation (Chung & Martin, 2002). However, since researchers cannot ethically force participants to consume alcohol and volunteers can be difficult to find, most studies involving alcohol consumption are performed on rats.

Other impairments or injuries in the hippocampus can also lead to decreased spatial processing ability. Human adults who lose neuronal volume in the hippocampus (hippocampal atrophy), experience impairments with spatial processing (Schautzer, Hamilton, Kalla, Strupp, & Brandt, 2003; Brandt et al., 2005). Alzheimer's disease is typically associated with hippocampal atrophy, in which the hippocampus loses both neurons and overall volume due to the formation of neurofibrillary tangles (Zarow, Wang, Chui, Weiner, & Csernansky, 2011). Indeed, mild cognitive impairments in individuals who exhibit hippocampal atrophy predict the development of Alzheimer's disease (Henneman et al., 2009). Early in Alzheimer's disease progression, hippocampal volume is the most sensitive measure in determining the stage of memory loss, but as the disease develops overall brain volume is more predictive of the level of impairment (Henneman et al., 2009). Additionally, in an isolated case study, a man who suffered a stroke sustained right posterior hippocampal damage and was consequently unable to find his way to the place he had worked for the last 20 years, further suggesting that the posterior hippocampus is related to spatial navigation/processing skills (Aradillas, Libon, & Schwartzman, 2011).

Spatial Memory Deficits

Moreover, hippocampal reduction or destruction can also result in memory impairments, including the inability to form new memories or remember recent events (Bird & Burgess, 2008). Researchers first discovered this connection between the hippocampus and memory impairment

from a case study of patient H.M (Squire, 2009). Patient H.M. suffered from epileptic seizures, which originated from the hippocampus upon further investigation. Doctors bilaterally removed patient H.M.'s bilateral hippocampi and surrounding regions, which resulted in anterograde amnesia: the inability to form new memories (Squire, 2009). To invoke anterograde amnesia, both hippocampi must be removed since patients who had only one temporal lobe removed showed no memory impairments (Squire, 2009). Consequently, this suggests that bilateral removal of the hippocampus, rather than one hemisphere, is associated with memory loss (Squire, 2009). Additionally, Bonner-Jackson, Mahmoud, Miller, and Banks (2015) determined that patients with Alzheimer's disease, and thus significant memory impairment, had smaller hippocampal volume compared to typically developing controls. As memory impairment gradually increased, hippocampal volume decreased. Upon damage to the hippocampus, including the reduction in overall hippocampal volume, patients exhibit symptoms of memory loss, suggesting that the hippocampus is implicated in memory.

Division of the Hippocampus into Distinct Regions

Recent studies on rodents and humans suggest that the hippocampus is not one unitary structure, but rather the anterior and posterior regions of the hippocampus are related to different functions, specifically spatial ability and emotional regulation (McHugh et al., 2010). McHugh et al. (2010) used rats to examine the function of specific regions in the hippocampus and predicted that the posterior hippocampus is involved with spatial learning, whereas the anterior hippocampus is involved with anxiety. Rats were given tasks to induce anxiety and measure spatial processing ability, and were evaluated according to changes in brain tissue oxygen levels. In order to elicit anxiety, the researchers placed the rats in novel environments and timed how long it took the rat to eat the provided food, assuming that more anxious rats took a longer time

to begin eating (McHugh et al., 2010). The spatial processing task did not constitute inducing anxiety; rather, it involved placing rats in a maze that contained food and timing the subsequent trials to test the rat's efficiency for finding the food (McHugh et al., 2010). The researchers discovered a double dissociation: blood oxygen levels rose substantially from the baseline in the posterior hippocampus compared to the anterior hippocampus during the spatial navigation task, in which rats navigated their way through a maze to find food. In the anterior hippocampus, blood oxygen levels increased significantly when rats were undergoing the anxiety inducing task. Furthermore, Goodrich-Hunsaker et al. (2005) found that when lesions were made on the posterior hippocampus, the rats could no longer determine how far apart the blocks of cheese were from one another. This suggests that environmental cues are necessary for rodents to determine physical distances between objects or locations, insinuating an association between the posterior region of the hippocampus and spatial processing skills (Goodrich-Hunsaker et al., 2005).These studies helped pave the way for human structural MRI studies, in which the hippocampus was demarcated into anterior and posterior regions.

Human behavior is indeed predicted based on varying volumes of the anterior and posterior regions of the hippocampus (Daugherty, Yu, Flinn, & Ofen, 2015). Premature individuals have a smaller posterior hippocampus, which could lead to worse verbal learning in adolescence (Giminez et al., 2004). The posterior region of the hippocampus is also significantly smaller in individuals with post-traumatic stress disorder (PTSD), suggesting that the posterior region becomes smaller due to the consequences of PTSD victims' exaggerated fear response (Bonne et al., 2008). Schizophrenic individuals also have reduced posterior hippocampal volume, and while the reason for this decreased volume is unclear, it suggests there may be altered brain functioning in the posterior hippocampus (Benes et al., 1991; Adriano, Caltagirone,

& Spalletta, 2012). Additionally, individuals diagnosed with hippocampal sclerosis (Longoni et al., 2013) and Alzheimer's disease (Gordon et al., 2013) have reduced anterior hippocampal volume. However, it would appear that the posterior region of the hippocampus is implicated in spatial memory, as opposed to the anterior region (Maguire et al., 2000). Maguire et al. (2000) found a relation between spatial memory ability and enlarged posterior hippocampal volume by evaluating MRI scans from experienced taxi drivers (assumed to have comprehensive spatial memory ability) and control participants who do not drive taxis. Moreover, source memory, which refers to the retrieval of contextual information (Tulving, 1985), was positively related to bilateral posterior hippocampal volume but not anterior hippocampal volume, suggesting that the posterior region of the hippocampus is more involved with memory than the anterior region of the hippocampus (Poppenk & Moscovitch, 2011). Since the hippocampal regions function in differing aspects of human behavior and the size of different hippocampal sub regions can be tied to specific psychopathology, the hippocampus can be logically demarcated into distinct regions that should exhibit functional specialization.

Based on previous literature which indicates human hippocampi functions are closely related to those of rodents (Jones & Wilson, 2005; Wolbers et al., 2007), the current study predicted an association between bilateral posterior and middle hippocampal regions and spatial processing deficits such that decreased hippocampal volume would result in more severe spatial processing deficits. The middle region of the hippocampus has recently been recognized as a distinct third region of the hippocampus, so little research exists regarding its association with cognitive measures (Daugherty et al., 2015). The current study believes the middle region has distinct functions separate from the anterior and posterior regions of the hippocampus based on research by Daugherty et al. (2015), leading to the hypothesis that this region would be involved

with spatial processing, such that smaller bilateral middle hippocampal volume would be associated with worse scores on spatial processing measures. As evidenced by previous literature, it was expected that the posterior region would be more so involved with spatial representation (McHugh et al., 2010) compared to the anterior region, and the middle region of the hippocampus was a focus in the hypothesis as well.

Hypotheses

Hypothesis 1: Lower total hippocampal volume will be positively related to lower scores on the spatial processing measures Block Design, VMI, Design Fluency, and Visual Attention.

Hypothesis 2: Anterior hippocampal volume will not be significantly related to scores on the spatial processing measures Block Design, VMI, Design Fluency, and Visual Attention, as the anterior region does not appear to be related to spatial processing.

Hypothesis 3: There will be a significant positive relationship between middle hippocampal volume and scores on the spatial processing measures, such that children with smaller middle hippocampal volume will have significantly lower scores on Block Design, VMI, Design Fluency, and Visual Attention.

Hypothesis 4: There will be a significant positive relationship between posterior hippocampal volume and scores on the spatial processing measures, such that children with smaller posterior hippocampal volume will have significantly lower scores Block Design, VMI, Design Fluency, and Visual Attention

Method

Participants

The participants in this study were part of a larger study conducted at a Child Clinical Neuropsychology Laboratory at a large Midwestern university funded by the National Institute

of Health (R03 HD048752 and R15 HD065627). The lab concentrates on the association between anatomical brain structures and neuropsychological capacity in children with ADHD, RD, comorbid ADHD/RD, and typically developing controls.

Two hundred and eighty-four children from the ages of 8 through 12 years participated in the larger project and about 150 completed MRI scanning. MRI scans from 136 participating individuals were used in the current study, 87% of whom identified as Caucasian, 4% identified as African/African American and Hispanic/Spanish/Latino, 5% of whom identified as other ethnicity, and less than 1% of whom identified as Asian/Asian American. Additionally, of the participating individuals, 37 were typically developing controls (27%), 20 were diagnosed with RD and comorbid ADHD/RD (15% each), 56 were diagnosed with ADHD (41%), and 4 were diagnosed with another attention disorder (2%). Diagnosis was determined by a child clinical neuropsychologist. The participants with scans who were not included in the study either had sufficient motion artifact in their scans to prevent tracing or were collected after the student left who was conducting the actual tracing of the structure.

Measures

Wechsler Intelligence Scale for Children – Third Edition (WISC-III; Wechsler, 1991). The WISC-III was used prior to 2006 as a measure of intellectual functioning. A Full-Scale Intelligence Quotient (FSIQ) is computed from four index scores that measure different aspects of intelligence: Verbal Comprehension Index (VCI), Perceptual Organization Index (POI), the Freedom from Distractibility Index (FDI), and the Processing Speed Index (PSI). All Index scores have a mean of 100 and a standard deviation of 15. Individual subtests have a mean of 10 with a standard deviation of 3.

The FSIQ of the WISC-III has a concurrent validity correlation of .96 with the previous version, the WISC-R (Wechsler, 1991; Wechsler, 1974). The test-retest reliability coefficient for the FSIQ in a sample of children ages 10-11 years is .95. The POI measures nonverbal reasoning and visual-spatial processing, and is comprised of the following 48 subtests: Picture Completion, Picture Arrangement, Block Design, and Object Assembly. The POI has a split-half reliability for children and adolescents ages 6-16 years of .90 and a test-retest reliability for children ages 10-11 years of .87. The WISC was used to ensure no participants have mental retardation.

***Block design*.** This subtest assesses the ability to analyze and recreate visual stimuli using blocks. Within a 1-minute time limit, participants are shown a model or picture of different block groupings and are instructed to recreate that image with their own red and white blocks. The patterns become increasingly difficult until a ceiling is met. Scoring ranges from 0-4, with 4 being *completely correct* and 0 being *incorrect*. Time bonuses are given within this framework when participants are correct. For children and adolescents between 8 to 16 years of age the mean reliability is .92 (Kaplan, Fein, Morris, Kramer, & Delis, 1999).

A Developmental Neuropsychological Assessment (NEPSY; Korkman, Kirk, & Kemp, 1998). The NEPSY is comprised of subtests that assess five functional domains that measure different aspects of neuropsychological functioning: Attention/Executive Functions, Language, Sensorimotor Functions, Visuospatial Processing, and Learning and Memory. All functional domain scores have a mean of 100 and a standard deviation of 15. Select subtests from the Attention/Executive Functions domain of the NEPSY were administered as measures of executive functioning, including Design Fluency and Visual Attention (Korkman, Kirk, & Kemp, 1998). The scores for Design Fluency and Visual Attention are reported with a mean of 100 and a standard deviation of 15.

The internal consistency reliability coefficient for the NEPSY in a sample of children ages 3-16 years ranges from .70 to .91 (Korkman et al., 1998). The internal consistency reliability coefficient for the Attention/Executive Functions domain in a sample of children ages 5-8 years ranges from .83 to .87 (Korkman et al., 1998).

Design fluency. This subtest assesses the ability to create as many unique designs as possible by connecting up to 5 dots presented in two arrays: structured and random. Children are instructed to generate as many novel designs as possible within a 1-minute period of time for each array. Only novel designs are given credit. The Design Fluency subtest has an internal consistency of .59 for children 5-12 years of age (Korkman et al., 1998).

Visual attention. This subtest assesses the speed and accuracy with which a child is able to focus selectively on, and maintain attention to, visual targets within an array. Children are instructed to cross out all visual stimuli within 180 seconds that match the target visual stimuli, and not the distractor items. The stimuli changes depending on the child's age: children ages 3-4 are shown bunnies and cats, while children ages 5-12 are shown cats and faces. All of the participants in this study were shown cats and faces. The Visual Attention subtest has an internal consistency of .62 for children 5-12 years of age (Korkman et al., 1998).

Beery-Visual Motor Integration – Fifth Edition (Beery-VMI; Beery & Beery, 2004). The Beery-VMI (fifth edition) was used to identify children who have not fully integrated their visual and motor abilities (Beery & Beery 2004). The pediatric version of the Beery-VMI (fifth edition) is for children and adolescents ages 2 to18 years. Participants are shown a sequence of 30 geometric shapes and are instructed to copy the shapes using pencil and paper. They are only allowed one try per figure and are not allowed to erase. Beery and Beery (2004) reported that

inter-rater reliability ranged from 0.92 to 0.98 and test–retest reliability correlation is 0.92 for a 2-week interval.

Procedure

Informed consent was given by the child's parent or guardian before the study commenced, and the family received a free neuropsychological report on their child as compensation. The child received a free lab t-shirt for participating. All measures were carried out in a quiet room in the Child Clinical Neuropsychology Laboratory, and testing lasted around nine hours.

The MRI scan was conducted on a separate day. A 1.5 Tesla Philips Intera scanner was used to obtain structural MRI scans for this study. Children were scanned for approximately 8 minutes in the local hospital scanner. Participants were scheduled by the Child Clinical Neuropsychology Laboratory, and steps were taken to reduce the children's apprehension about the scanner and motion artifacts. Once the scanning was completed, the participants were allowed to leave to hospital and the images were sent to the Child Clinical Neuropsychology Laboratory. The cost of the scan was paid for by NIH grants awarded to the principal investigator. The images were then loaded into Analyze software version 10.0 where the MRI scans were aligned using Analyze according to the AC-PC (anterior commissure-posterior commissure) axis, the longitudinal fissure, and the optic area in order to establish the same orientation for all of the brains in all planes. All brains were checked throughout the alignment process to ensure accuracy.

Hippocampus tracing. The hippocampus was previously traced and segmented into anterior and posterior regions by a former graduate student in the Child Clinical Neuropsychology Laboratory (Lee, 2011). I sliced a third region of the hippocampus, splitting

the posterior region of the hippocampus into the posterior and middle regions of the hippocampus manually using Analyze 10.0. The measurement of the third demarcation of the hippocampus was based on guidelines ascertained by Daugherty et al. (2015). The slice was made in the coronal plane, one slide before the pulvinar of the thalamus was no longer visible. Once the slice was made in the coronal plane, the new three-part split of the hippocampus was visualized in the sagittal plane to check that the demarcation was in line with the anatomical boundaries described by Daugherty et al. (2015). Specifically, I looked for the point where the fornix extended behind the pulvinar, and if that point separated the posterior region of the hippocampus from the middle region of the hippocampus. Both hemispheres were regarded in the same manner.

Before I began this experiment, I obtained inter-rater reliability with a doctoral student in the lab of at least .90. To attain this, we each segmented 10 brains independently until inter-rater reliability was established. Pearson correlations between each segmenter's three hippocampal sub regions were used to calculate inter-rater reliability coefficient of r = .94 for the right middle, r = .92 for the right posterior, r = .98 for the left middle, and r = .93 for the left posterior. Once completed, I re-sliced any of the hippocampi that were not reliably measured during inter-rater reliability. I re-segmented 10 brains for an intra-reliability coefficient of r = .98 and higher for the left and right middle and posterior portions of the hippocampus. All brain measurements were traced and segmented blind to group membership.

Results

Preliminary Analyses

Preliminary analyses included an examination of frequency distributions for demographic variables (i.e., gender, age, socioeconomic status, ethnicity, and FSIQ), hippocampus volumes, and measures of cognitive ability (i.e., Block Design, VMI, Design Fluency, and Visual Attention). See Table 1 for demographic variables.

A Pearson correlation was calculated to control for FSIQ and total brain volume as they relate to the dependent variables Design Fluency, Block Design, Visual Attention, and DTVMI. Results indicated that FSIQ was significantly correlated with Design Fluency, but there was not a significant correlation with total brain volume. Results also indicated that FSIQ was not significantly correlated with Block Design, nor was there was a significant correlation with total brain volume. Results indicated that FSIQ was significantly correlated with Visual Attention, but there was not a significant correlation with total brain volume. Results also indicated that FSIQ was significantly correlated with DTVMI, but there was not a significant correlation with total brain volume. See Table 2 for correlation values.

Design Fluency

A simple linear regression was calculated to predict Design Fluency based on right and left total hippocampal volume. Results indicated hippocampal volume was a significant predictor, $F(4, 128) = 15.77$, $p = .001$, adjusted $R^2 = .183$. Including the control variables FSIQ and total brain volume, adjusted $R^2 = .225$, R^2 change = .053, $F(4, 128) = 10.57$, significant F change, $p = .013$, indicating adding these variables significantly improved the model. A simple linear regression was calculated to predict Design Fluency based on right and left anterior

hippocampal volume. Results indicated hippocampal volume was a significant predictor, $F(4, 128) = 15.77$, $p = .001$, adjusted $R^2 = .183$. Including the control variables FSIQ and total brain volume, adjusted $R^2 = .213$, R^2 change = .041, $F(4, 128) = 9.91$, significant F change, $p = .035$, indicating adding these variables significantly improved the model. A simple linear regression was calculated to predict Design Fluency based on right and left middle hippocampal volume. Results indicated hippocampal volume was a significant predictor, $F(4, 128) = 15.77$, $p = .001$, adjusted $R^2 = .183$. However, including the control variables FSIQ and total brain volume did not improve the equation, adjusted $R^2 = .198$, R^2 change = .027, $F(4, 128) = 9.15$, no significant F change, $p = .111$. A simple linear regression was calculated to predict Design Fluency based on right and left posterior hippocampal volume. Results indicated hippocampal volume significantly predicted scores on Design Fluency, $F(4, 128) = 15.77$, $p = .001$, adjusted $R^2 = .183$. Including the control variables FSIQ and total brain volume, adjusted $R^2 = .248$, R^2 change = .075, $F(4, 128) = 11.88$, significant F change = .002, $p < .001$, indicating adding these variables significantly improved the model. See Table 3 for β values for this regression analysis.

Block Design

A simple linear regression was calculated to predict Block Design based on left and right total hippocampal volume. The results of the regression equation were not significant, $F(3, 129) = .057$, $p = .812$, adjusted $R^2 = -.007$. Including the control variable total brain volume did not improve the equation, adjusted $R^2 = -.012$, R^2 change = .010, $F(3, 129) = 11.88$, no significant F change, $p = .512$. A simple linear regression was calculated to predict Block Design based on right and left anterior hippocampal volume but was not significant, $F(3, 129) = .057$, $p = .812$, adjusted $R^2 = -.007$. Including the control variable total brain volume, adjusted $R^2 = -.016$, R^2 change = .007, $F(3, 129) = .320$, no significant F change, $p = .637$, was noted. A simple linear

regression was calculated to predict Block Design based on right and left middle hippocampal volume with no significant finding, $F(3, 129) = .057$, $p = .812$, adjusted $R^2 = -.007$. Including the control variable total brain volume did not improve the equation, adjusted $R^2 = -.018$, R^2 change = .005, $F(3, 129) = .220$, no significant F change, $p = .739$. A simple linear regression was calculated to predict Block Design based on right and left posterior hippocampal volume with no significant result, $F(3, 129) = .057$, $p = .812$, adjusted $R^2 = -.007$. Including the control variable total brain volume did not improve the equation, adjusted $R^2 = -.006$, R^2 change = .017, $F(3, 129) = .750$, no significant F change, $p = .337$, no improvement was noted. See Table 4 for β values for this regression analysis.

Visual Attention

A simple linear regression was calculated to predict Visual Attention based on left and right total hippocampal volume. A significant regression equation was noted, $F(4, 128) = 3.39$, $p = .037$, adjusted $R^2 = .035$, indicating total hippocampal volume predicted scores in Visual Attention. Including the control variables FSIQ and total brain volume improved the model, adjusted $R^2 = .063$, R^2 change = .042, $F(4, 128) = 3.23$, approaching significance F change = .055, $p = .001$. A simple linear regression was calculated to predict Visual Attention based on left and right anterior hippocampal volume. A significant regression equation was found, $F(4, 128) = 3.39$, $p = .037$, adjusted $R^2 = .035$, indicating anterior hippocampal volume was a significant predictor. Including the control variables FSIQ and total brain volume the equation improved, adjusted $R^2 = .069$. R^2 change = .047, $F(4, 128) = 3.43$, significant F change, $p = .038$. A simple linear regression was calculated to predict Visual Attention based on left and right middle hippocampal volume. A significant regression equation was noted, $F(4, 128) = 3.39$, $p = .037$, adjusted $R^2 = .035$. Including the control variables FSIQ and total brain volume did not improve

the equation, adjusted R^2 = .020, R^2 change = .001, F(4, 128) = 1.68, no significant F change, p = .984. A simple linear regression was calculated to predict Visual Attention based on left and right posterior hippocampal volume. A significant regression equation was found, F(4, 128) = 3.39, p = .037, adjusted R^2 = .035. Including the control variables FSIQ and total brain volume, adjusted R^2 = .072, R^2 change = .050, F(4, 128) = 3.54, no significant F change, p = .031. See Table 5 for β values for this regression analysis.

Developmental Test of Visual Motor Integration (DTVMI)

A simple linear regression was calculated to predict DTVMI based on left and right total hippocampal volume. The results indicated total hippocampal volume significantly predicted scores on DTVMI, F(4, 128) = 5.23, p = .007, adjusted R^2 = .060. Including the control variables FSIQ and total brain volume did not significantly improve the equation, adjusted R^2 = .065, R^2 change =.019, F(4, 128) = 3.30, no significant F change, p = .263. A simple linear regression was calculated to predict DTVMI based on left and right anterior hippocampal volume, and results indicated anterior volume was a significant predictor, F(4, 128) = 5.23, p = .007, adjusted R^2 = .060. Including the control variables FSIQ and total brain volume did not improve the model, adjusted R^2 = .055, R^2 change = .010, F(4, 128) = 2.94, no significant F change, p = .511. A simple linear regression was calculated to predict DTVMI based on left and right middle hippocampal volume. Results indicated middle hippocampal volume significantly predicted scores on DTVMI, F(4, 128) = 5.23, p = .007, adjusted R^2 = .060. After including the control variables FSIQ and total brain volume, no improvement was noted, adjusted R^2 = .053, R^2 change = .008, F(4, 128) = 2.86, no significant F change, p = .590. A simple linear regression was calculated to predict DTVMI based on left and right posterior hippocampal volume. A significant regression equation was found, F(4, 128) = 5.23, p = .007, adjusted R^2 = .060,

indicating posterior hippocampal volume predicted DTVMI. Including the control variables FSIQ and total brain volume produced no improvement in the equation, adjusted R^2 = .074, R^2 change = .028, $F(4, 128) = 3.65$, no significant F change, $p = .139$. See Table 6 for β values for this regression analysis.

Discussion

The current study's first hypothesis postulated that lower total bilateral hippocampal volume was related to poorer scores on spatial processing measures Design Fluency, Visual Attention, DTVMI, and Block Design. Total hippocampal volume significantly predicted scores on all the spatial processing measures except Block Design. Thus, the results indicate that individuals with lower bilateral total hippocampal volume performed worse on spatial processing measures than individuals with a higher bilateral total hippocampal volume. Previous literature indicates that hippocampal volume is associated with spatial memory performance (Squire, 2009; O'Keefe & Nadel, 1978; Kumaran & Maguire, 2005; Hoscheidt et al., 2010; Goel et al., 2004). Bonner-Jackson et al. (2015) demonstrated that patients diagnosed with Alzheimer's disease, and thus exhibit significant memory impairment, had lower total hippocampal volume compared to individuals without Alzheimer's disease. The results from our study indicate that lower total hippocampal volume may be related to lower scores on spatial memory, which supports the current literature on total hippocampal volume and spatial memory.

The second hypothesis predicted that bilateral anterior hippocampal volume would not be related to scores on spatial processing measures based on McHugh and colleagues' (2010) research, which indicated that the anterior hippocampus is implicated in emotional regulation

rather than spatial processing. However, bilateral anterior hippocampal volume was a significant predictor for spatial processing measures except Block Design in the current study, so there may be an association between anterior hippocampal volume and spatial processing. Perhaps, emotional regulation includes some aspects of spatial processing. Holmes, Vuilleumier, and Eimer (2003) conducted an ERP study to determine a possible relationship between processing emotional expressions of individual faces and spatial attention. Individuals were shown images of facial expressions (neutral and fearful) from a standard measure of facial affect (Ekman & Friesen, 1976). Pictures of houses were paired with facial expressions to establish spatial attention. During each trial, participants were shown two images of facial expressions and two images of houses. Paired stimuli (i.e., the two houses) were shown either in vertical or horizontal pairs. Prior to each trial, a cue directed the participant's attention to either the paired horizontal or paired vertical stimuli. After viewing the stimuli, participants pressed a key whenever the two stimuli were identical (i.e., both houses). ERPs on faces-cued trials were compared to ERPs on houses-cued trials to determine if emotionally relevant stimuli is affected by spatial attention. During trials in which cued locations contained fearful facial expressions, frontal lobe activation increased. Conversely, when the facial expressions were neutral or were not cued, the frontal lobe effects were eliminated. These results indicate that processing emotional stimuli can be affected by spatial attention. Holmes and colleagues (2003) provide evidence that emotional regulation may be related to spatial processing, supporting the results of the current study's finding that anterior hippocampal volume is a significant predictor of an individual's score on measures of spatial processing.

Next, the current study's third hypothesis proposed that bilateral middle hippocampal volume would be related to an individual's score on spatial processing measures. Bilateral

middle hippocampal volume was a significant predictor of the spatial processing measures except Block Design. This finding is novel as no other research has determined an association between middle hippocampal volume and measures of spatial processing. Daugherty et al. (2015) was perhaps the first study to delineate the middle region of the hippocampus, demonstrating that it may be related to functions separate from the anterior and posterior regions of the hippocampus.

Finally, the current study's fourth hypothesis asserted that bilateral posterior hippocampal volume would be related to an individual's score on spatial processing measures. Our results supported this hypothesis; bilateral posterior hippocampal volume was a significant predictor of scores on the spatial processing measures except for Block Design. Evidence by McHugh et al. (2010), Goodrich-Hunsaker et al. (2005), and Maguire et al. (2000) indicates that the posterior region of the hippocampus is involved with spatial processing as opposed to the anterior region of the hippocampus; therefore we assumed that posterior hippocampal volume would be related to measures of spatial processing. Our results strengthen prior literature providing evidence that the posterior region of the hippocampus is involved in spatial processing.

Our findings indicated that hippocampal volume was predictive of all spatial processing measures but Block Design. Block Design is part of the Perceptual Reasoning subtest on the WISC-III, and it is the longest test within the subcategory (Raiford, Coalson, Saklofske, & Weiss, 2010). The participants in the current study consisted of children with various neurodevelopmental disorders, including ADHD and RD. One of the characteristic symptoms of ADHD is high distractibility (American Psychiatric Association, 2013). Perhaps, since the Block Design subtest was rather long, participants lost interest or were distracted by an object in the room or by the experimenter. Literature indicates that individuals with attention deficits may do

worse on measures of attention, including Block Design (Siegel & Ryan, 1989). If the participants stopped focusing on the subtest, their score may have lowered; thus, the score may not be due to hippocampal volume. Therefore, hippocampal volume may not be predictive of an ADHD participant's score on the Block Design subtest, contributing to the low predictive power of this spatial processing measure. Additionally, individuals with RD exhibit deficits in spatial processing, but no difficulty recalling nonverbal information (Kamhi, Catts, Mauer, Apel, & Gentry, 1988). Therefore, scores from individuals with RD may have also contributed to the finding that the independent variables were not predictive of Block Design.

The current study establishes an association between the regions of the hippocampus and an individual's score on spatial processing measures. However, there is also evidence that indicates different regions of the hippocampus may be associated with separate functions. Currently, little is known about the middle region of the hippocampus. Daugherty et al. (2010) found volumetric differences in the anterior, middle, and posterior hippocampus associated with age and sex, but neuropsychological tests were not administered to determine possible functional variations. Since Daugherty and colleague's (2010) study is perhaps the first to delineate the middle region of the hippocampus, research regarding the middle region's role is severely limited. Because middle hippocampal volume poorly predicted spatial processing in the current study, future investigations should focus on other types of memory that do not involve spatial information, (e.g., verbal memory) as literature indicates that the posterior region of the hippocampus is significantly related to verbal memory, while the anterior region of the hippocampus is not (Fernández et al., 1998). Therefore, the different types of memory that involve the hippocampus may be associated with distinct volumetric regions. Perhaps the middle region of the hippocampus has a more significant relationship to verbal memory rather than

spatial memory. Additionally, the finding indicating that the anterior region of the hippocampus was associated with spatial processing, which is not supported by prior literature (McHugh et al., 2010) is notable. Perhaps different measures of spatial processing could be used to determine if the anterior and middle hippocampal regions are indeed associated with spatial processing. For instance, the Spatial Relations Test (Thurstone & Thurstone, 1963) for children ages 8-12 involves the ability to discriminate shape from four alternatives that form a cube when combined with the first figure in each row; participants are given six minutes to finish 25 items. The Spatial Relations Test may be another valid measure of spatial processing that is more sensitive to variations in hippocampal volume, which could be used to validate the current study's findings that both anterior and middle hippocampal volume are associated with scores on measures of spatial processing.

Additionally, the current study included data from a diverse group of participants, all of whom were not typically developing controls; most of the participants had been diagnosed with ADHD, RD, or comorbid ADHD/RD. Since spatial attention may be associated with attention deficits demonstrated in ADHD (American Psychiatric Association, 2013), individuals with ADHD may exhibit variations in hippocampal volume compared to individuals with RD. Future studies should describe potential differences in the hippocampus-spatial processing/memory relationship between groups of children with neurodevelopmental disorders. Furthermore, right and left hemisphere differences exist in terms of function and structural connectivity, but the current study chose to focus on the whole region (i.e., total, anterior, middle, or posterior hippocampal volume) excluding hemispheric differences. Considering this, future studies may want to explore the possibility of one hemisphere possessing a stronger association with spatial processing compared to the other. For example, right hippocampal volume appears to be a

significant predictor of spatial location, which suggests that there are differences between right and left hippocampal functions (de Toledo-Morrell et al., 2000). Based on our results, we conclude there may be differences in children with ADHD and RD regarding scores obtained on measures of spatial processing and that anterior and middle hippocampal volume may be associated with spatial processing, despite prior research not validating either of these findings.

Overall, the current study's results indicated that total, anterior, middle, and posterior hippocampal volume were significant predictors of scores on all the spatial processing measures except Block Design. The finding that bilateral posterior hippocampal volume was a significant predictor for spatial processing measures was comparable with prior research with regards to posterior hippocampal volume and functionality (McHugh et al., 2010), as well as bilateral total hippocampal volume being a significant predictor of spatial processing (Squire, 2009; O'Keefe & Nadel, 1978; Kumaran & Maguire, 2005; Hoscheidt et al., 2010; Goel et al., 2004)). However, we discovered a significant relationship between anterior hippocampal volume and spatial processing, which had not been determined by previous literature (McHugh et al., 2010). The current study also found that bilateral middle hippocampal volume was a significant predictor of spatial processing scores, and this new finding adds to the current literature. The current study and one conducted by Daugherty et al. (2015) validate the claim that the middle region of the hippocampus is associated with certain functions along with the anterior and posterior regions of the hippocampus. Since the middle region of the hippocampus has not received much attention in prior research, it is an excellent candidate for studying subsequent functions in the future.

The current study's results indicate regions of the hippocampus may be associated with spatial processing, which emphasizes the importance of the different regions of the hippocampus. Spatial processing is a necessary skill acquired through normal human development. Failure to

develop essential spatial processing skills leads to complications later in life, including difficulty reading, engaging in physical activities, and solving mathematical equations (Mazzocco et al., 2006). Therefore, developing spatial processing skills is vital to an individual's ability to perform well in an educational setting as well as for extracurricular activities important for sustaining physical and mental health, such as regular exercise. The purpose of the current study was to expand the literature surrounding the volumetric studies conducted on the hippocampus as well as functional studies investigating which regions are responsible for specific functions. As a result, we were able to provide evidence regarding why the middle region of the hippocampus should be considered separate from the anterior and posterior hippocampal regions as well as substantiate literature indicating that the regions of the hippocampus may be associated with the same or similar functions.

Table 1

Demographic variables

Variables	N	Minimum	Maximum	Mean	Std. Deviation
Age	137	8	12	9.48	1.378
FSIQ	137	62	171	96.36	15.616
Socioeconomic status	137	12.0	69.0	39.814	12.7069
Ethnicity	137	118 Caucasians	5 African Americans	14 other ethnicities	
Gender	137	65 females			

Table 2

Correlations between Design Fluency, Block Design, Visual Attention, and DTVMI and FSIQ and total brain volume

		FSIQ	Total Brain Volume	Block Design	Design Fluency	Visual Attention	DTVMI
FSIQ	Pearson correlation	1	.075	-.028	.445	.245	.382
	Sig.		.388	.747	.000***	.004**	.000***
	N	137	134	137	137	137	137
Total brain volume	Pearson correlation	.075	1	.020	.080	-.034	.045
	Sig.	.388		.815	.359	.696	.602
	N	134	134	134	134	134	134
Block Design	Pearson correlation	-.028	.020	1	.003	-.044	.001
	Sig.	.747	.815		.977	.612	.989
	N	137	134	137	137	137	137
Design Fluency	Pearson correlation	.445	.080	.003	1	.102	.279
	Sig.	.000***	.359	.977		.233	.001***
	N	137	134	137	137	137	137
Visual Attention	Pearson correlation	.245	-.034	-.044	.102	1	-.011
	Sig.	.004**	.696	.612	.233		.898
	N	137	134	137	137	137	137
DTVMI	Pearson correlation	.382	.045	.001	.279	-.011	1
	Sig.	.000***	.602	.989	.001***	.898	
	N	137	134	137	137	37	137

** $p < .01$

*** $p < .001$

Table 3

Hippocampal volume effects on Design Fluency

		Unstandardized β	Coefficients Standard Error	Standardized Coefficients β	*t*	*p*
Model 1	Constant	50.733	10.134		5.006	.000***
	FSIQ	.404	.073	.440	5.521	.000***
	Total Brain Volume	$7.323 \times E^{-7}$	.000	.008	.104	.918
Model 2: Total Hippo-campus	Constant	33.243	11.486		2.894	.004**
	FSIQ	.378	.073	.412	5.177	.000***
	Total Brain Volume	$-7.436 \times E^{-7}$	.000	-.008	-.107	.915
	Right Total Hippocampus	.002	.003	.074	.628	.531
	Left Total Hippocampus	.005	.003	.173	1.505	.135
Model 2: Anterior Hippo-campus	Constant	42.327	10.621		3.985	.000***
	FSIQ	.327	.074	.406	5.060	.000***
	Total Brain Volume	$1.806 \times E^{-6}$	.000	-.020	-.257	.798
	Right Anterior Hippocampus	.007	.004	.195	2.014	.046*
	Left Anterior Hippocampus	.001	.004	.022	.236	.814
Model 2: Middle Hippo-campus	Constant	45.591	11.508		3.962	.000***
	FSIQ	.393	.073	.429	5.400	.000***
	Total Brain Volume	$2.276 \times E^{-6}$	.000	.026	.324	.747
	Right Middle Hippocampus	-.008	.005	-.139	-1.495	.137
	Left Middle Hippocampus	.012	.006	.193	2.067	.041*

Model 2: Posterior Hippo-campus	Constant	41.753	10.141		4.117	.000***
	FSIQ	.360	.071	.393	5.043	.000***
	Total Brain Volume	1.841 x E^{-6}	.000	.021	.269	.788
	Right Posterior Hippocampus	.021	.010	.217	2.105	.037*
	Left Posterior Hippocampus	.006	.008	.082	.806	.422

* $p < .05$
** $p < .01$
*** $p < .001$

Table 4

Hippocampal volume effects on Block Design

		Unstandardized *β*	Coefficients Standard Error	Standardized Coefficients *β*	*t*	*p*
Model 1	Constant	9.120	95.382		.096	.924
	Total Brain Volume	1.877 x E^{-5}	.000	.021	.238	.812
Model 2: Total Hippo-campus	Constant	81.483	121.748		.669	.505
	Total Brain Volume	3.235 x E^{-5}	.000	.036	.404	.687
	Right Total Hippocampus	-.031	.035	-.113	-.860	.391
	Left Total Hippocampus	.004	.036	.015	.113	.910
Model 2: Anterior Hippo-campus	Constant	56.169	107.820		.521	.603
	Total Brain Volume	3.256 x E^{-5}	.000	.036	.404	.687
	Right Anterior Hippocampus	-.024	.042	-.061	-.564	.574
	Left Anterior Hippocampus	-.013	.042	-.034	-.316	.753
Model 2: Middle Hippo-campus	Constant	-7.138	118.808		-.060	.952
	Total Brain Volume	2.492 x E^{-5}	.000	.028	.312	.755
	Right Middle Hippocampus	-.040	.063	-.067	-.639	.524
	Left Middle Hippocampus	.047	.065	.075	.720	.472
Model 2: Posterior Hippo-campus	Constant	68.128	104.049		.655	.514
	Total Brain Volume	1.648 x E^{-5}	.000	.018	.206	.837
	Right Posterior Hippocampus	-.096	.115	-.098	-.832	.407
	Left Posterior Hippocampus	-.032	.091	-.041	-.350	.727

Table 5

Hippocampal volume effects on Visual Attention

		Unstandardized β	Coefficients Standard Error	Standardized Coefficients β	*t*	*p*
Model 1	Constant	-35.966	182.019		-.198	.844
	FSIQ	3.381	1.315	.223	2.572	.011*
	Total Brain Volume	.000	.000	-.071	-.813	.417
Model 2: Total Hippo-campus	Constant	-134.086	208.632		-.643	.522
	FSIQ	3.847	1.327	.254	2.900	.004**
	Total Brain Volume	-8.041 x E^{-5}	.000	-.055	-.639	.524
	Left Total Hippocampus	.134	.057	.297	2.356	.020*
	Right Total Hippocampus	-.122	.056	-.280	-2.167	.032*
Model 2: Anterior Hippo-campus	Constant	-5.275	190.899		-.028	.978
	FSIQ	4.097	1.322	.270	3.100	.002**
	Total Brain Volume	-9.822 x E^{-5}	.000	-.067	-.777	.438
	Right Anterior Volume	-.169	.066	-.269	-2.556	.012*
	Left Anterior Volume	.119	.066	.187	1.799	.074
Model 2: Middle Hippo-campus	Constant	-24.711	210.236		-.118	.907
	FSIQ	3.401	1.330	.224	2.556	.012*
	Total Brain Volume	.000	.000	-.072	-.819	.414
	Right Middle Volume	.010	.100	.010	.095	.942
	Left Middle Volume	-.018	.104	-.018	-.177	.859

Model 2: Posterior Hippo-campus	Constant	-171.051	186.205		-.611	.360
	FSIQ	2.872	1.312	.189	2.190	.030*
	Total Brain Volume	$-7.685 \times E^{-5}$	.000	-.006	-.074	.941
	Right Posterior Hippocampus	.176	.181	.111	.970	.334
	Left Posterior Hippocampus	.171	.142	.137	1.205	.230

* $p < .05$
** $p < .01$

Table 6

Hippocampal volume effects on DTVMI

		Unstandardized β	Coefficients Standard Error	Standardized Coefficients β	*t*	*p*
Model 1	Constant	70.775	9.209		7.685	.000***
	FSIQ	.212	.067	.273	3.194	.002**
	Total Brain Volume	$-2.265 \times E^{-7}$	.000	-.003	-.035	.972
Model 2: Total Hippo-campus	Constant	61.856	10.686		5.788	.000***
	FSIQ	.204	.068	.263	3.004	.003**
	Total Brain Volume	$-7.282 \times E^{-7}$	.000	-.010	-.113	.910
	Right Total Hippocampus	$-8.499 \times E^{-5}$	.003	-.004	-.029	.977
	Left Total Hippocampus	.003	.003	.142	1.124	.263
Model 2: Anterior Hippo-campus	Constant	67.004	9.857		6.798	.000***
	FSIQ	.212	.068	.273	3.109	.002**
	Total Brain Volume	$-1.469 \times E^{-6}$	.000	-.020	-.225	.822
	Right Anterior Hippocampus	$-2.857 \times E^{-5}$	.003	-.001	-.008	.993
	Left Anterior Hippocampus	.003	.003	.100	.958	.340
Model 2: Middle Hippo-campus	Constant	66.069	10.594		6.236	.000***
	FSIQ	.206	.067	.265	3.072	.003**
	Total Brain Volume	$2.166 \times E^{-6}$	.000	.003	.033	.973
	Right Middle Hippocampus	-.001	.005	-.016	-.156	.876
	Left Middle Hippocampus	.005	.005	.095	.940	.349

Model 2: Posterior Hippo-campus	Constant	67.721	9.532		7.105	.000***
	FSIQ	.188	.067	.241	2.794	.006**
	Total Brain Volume	$-4.790 \times E^{-7}$	.000	-.006	-.074	.941
	Right Posterior Hippocampus	.016	.009	.198	1.732	.086
	Left Posterior Hippocampus	-.003	.007	-.047	-.410	.683

** $p < .01$

*** $p < .001$

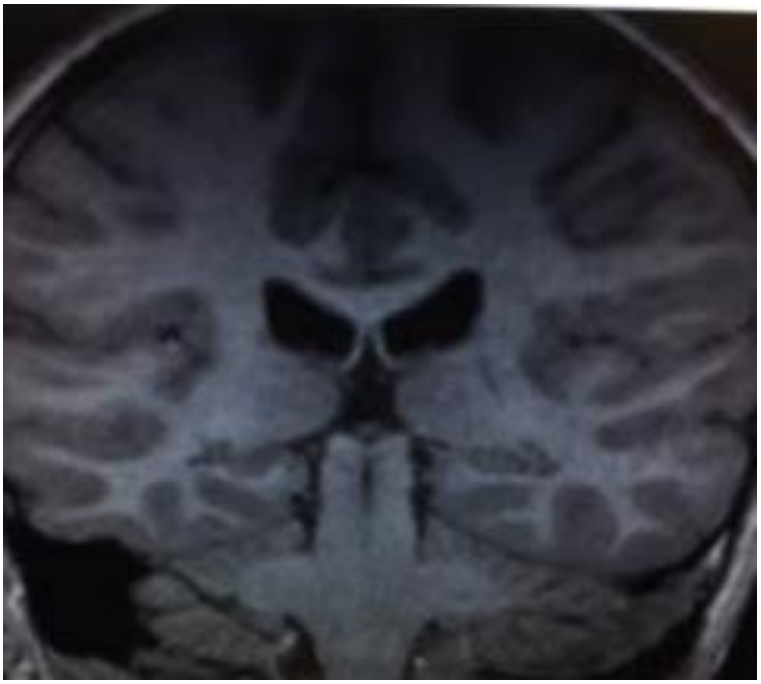

Figure 1. Pulvinar of thalamus still in view; MRI scan; coronal view

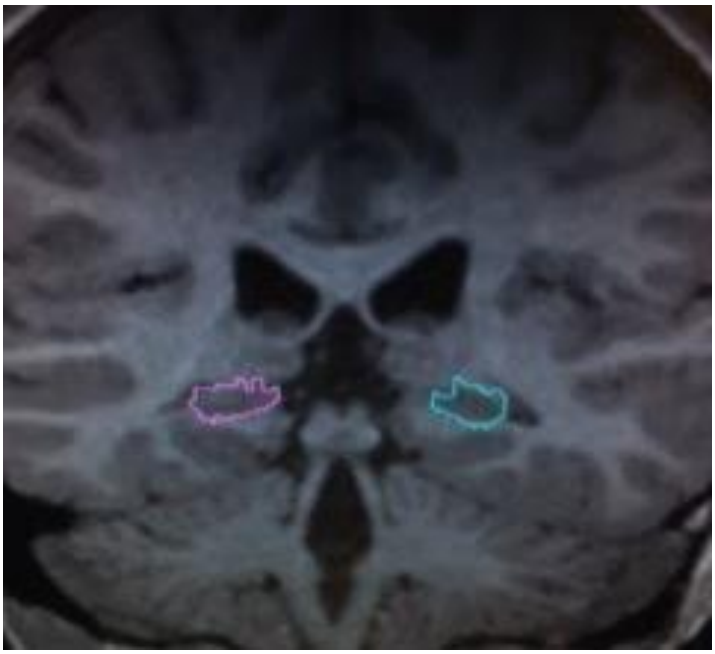

Figure 2. First slice of right/left middle hippocampus before disappearance of pulvinar; MRI scan; coronal view

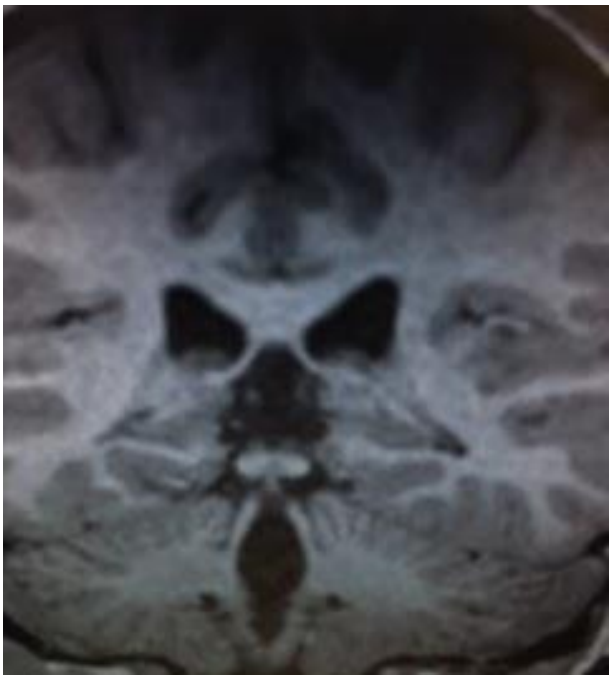

Figure 3. Disappearance of pulvinar without tracing; MRI scan; coronal view

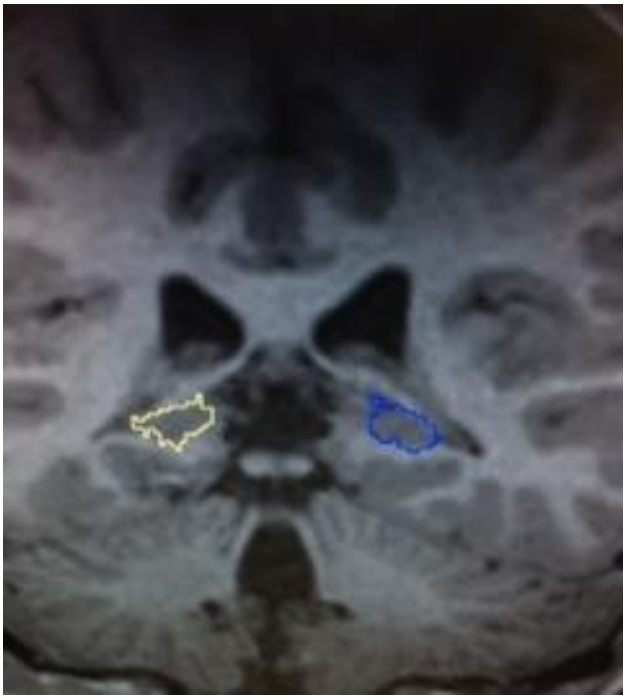

Figure 4. Disappearance of pulvinar with tracing; first slice right/left posterior hippocampus; MRI scan; coronal view

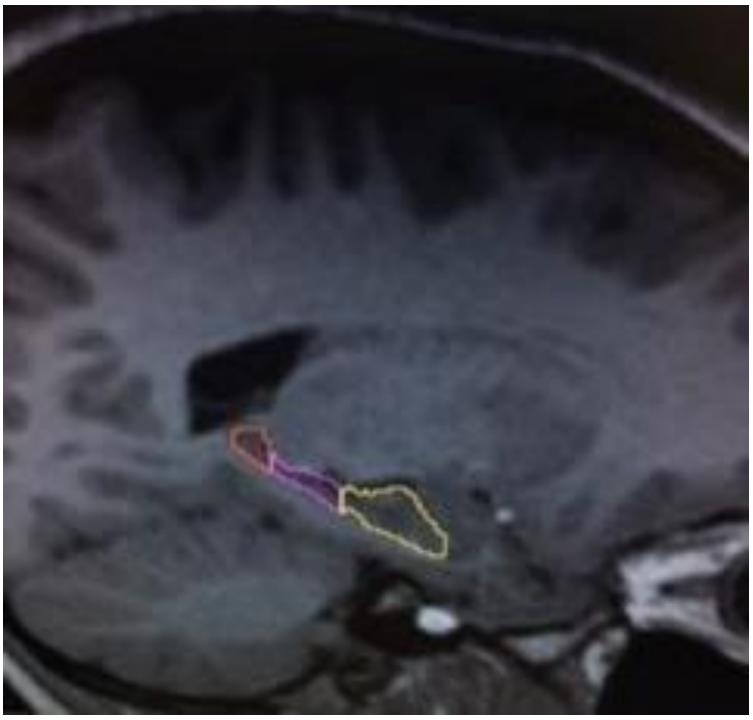

Figure 5. Verification of alignment; MRI scan; sagittal view

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