Spatial Memory Performance in Chronic Heart Failure

by

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DEDICATION

This dissertation is dedicated to my wonderful parents, step-parents, children, brother, step-sister, niece, nephews, my partner, and to my wonderful friends for all their encouragement and support.

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ABSTRACT

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Twenty five percent to 50% of heart failure (HF) patients have cognitive dysfunction, including spatial memory dysfunction (e. g. inability to find their way or remember where their belongings are usually kept), possibly due to cerebral hypoperfusion resulting in hippocampal injury. Spatial memory dysfunction decreases one's ability to function independently (e.g. navigate to familiar places). Using paper and pencil measures, visuospatial memory was demonstrated to be poorer in HF patients compared with healthy adults. However, literature about allocentric (relationship between objects in the environment) spatial memory in HF patients is limited.

Specific aims were to: 1) compare allocentric spatial memory of adults with and without HF; 2) determine relationships between allocentric and egocentric measures of spatial memory; and 3) examine the influence of gender, group, perceived cognitive activity, and perceived functional capacity on spatial memory.

Adults with HF (32) and healthy adults (32) were recruited at a Midwestern university. During two consecutive days, participants completed a virtual reality measure of spatial

memory and learning, and, tests of memory, attention, and executive function. Perceived cognitive activity and functional capacity were measured. A comparative design was used.

No significant difference in spatial memory and learning was found between groups although HF patients had poorer spatial memory and learning scores. Significant differences were found in spatial memory, using a mean score to decrease variance. Most correlations between allocentric (path length, time to target, and heading error) and egocentric measures (figure copy and figure memory recall, Corsi Block-tapping forward, Corsi Block-tapping backward) were non-significant. Gender, group, perceived cognitive activity, perceived functional capacity and age explained 13% of time spent in target quadrant (p = .020) and 4% of heading error (p = .184) during spatial memory testing. Age was the only significant independent predictor.

HF patients had worse spatial memory and learning compared with healthy adults when variance was decreased. Allocentric and egocentric measures of spatial memory have distinct properties and this should be considered in study design. Older age was a predictor of spatial memory performance in HF patients and healthy adults. Age is a known predictor but it may be related to an egocentric rather than an allocentric frame of reference. Future studies need to focus on other predictors of allocentric spatial memory.

CHAPTER I

Introduction

In the U.S., approximately 5.1 million Americans who are 20 years of age or older have chronic heart failure (referred to as HF in this paper) and this number is expected to increase 46% by 2030 (Go et al., 2014). A major consequence of HF is systemic hypoperfusion, which may lead to cerebral oxygen deprivation, hippocampal injury, and cognitive dysfunction, including spatial memory dysfunction (Hoth, Poppas, Moser, Paul, & Cohen, 2008; Newman & Kaszniak, 2000; Smith & Mizumori, 2006; Vogels, Oosterman, van Harten, Gouw et al., 2007; Woo, Macey, Fonarow, Hamilton, & Harper, 2003). Patients with spatial memory dysfunction (see table 1.1) present with the inability to learn and remember important places, find their way in familiar and unfamiliar surroundings, and remember where belongings have been placed or where they are usually kept (Spiers, Burgess, Hartley, Vargha-Khadem, & O'Keefe, 2001). Because the hippocampus is one of the structures within the brain most sensitive to oxygen deprivation, it is one of the first structures in the brain to be affected by cerebral hypoperfusion (Briones et al., 2004; Briones, Therrien, & Metzger, 2000). Thus, a reasonable biological explanation for the presence of spatial memory dysfunction in HF patients exists.

Wayfinding, the inability to find one's way within the environment without getting lost, is a component of spatial memory dysfunction (Davis, Therrien, & West, 2008). Most often, way-finding is accomplished by navigation using one of two frames of reference (allocentric, egocentric). Allocentric spatial memory uses the relationship between objects in the

environment, regardless of the individual's location (Aguirre & D'Esposito, 1999); for example, knowing the relationship of your doctor's office to your work office (given one cannot be seen from the other). Allocentric spatial memory may be accomplished using a cognitive map, which relies on direction, object relationships, and locations in the environment, to find one's way. Cognitive maps take more cognitive demand to develop but, once developed, are more flexible and efficient (Nadel & O'Keefe, 1978).

Egocentric spatial memory is being used when the relationship between an object and a goal is in immediate reference to the individual and spatial dimensions are visualized from the perspective (right, left, in front of, behind) of the individual (Aguirre & D'Esposito, 1999). O'Keefe and Nadel (1978) discussed problems that may occur when a route is used to navigate. Routes use landmarks and are based on an egocentric frame of reference. If an individual forgets a portion of the route or if a landmark changes in some way, it is very easy to become lost. In order to get to the intended location, the individual must first get back to the point at which the error was made in order to continue on the original route.

Table 1.1 Definitions for Components and Measurement of Spatial Memory

Concept	Conceptual Definition	Operational Definition
Allocentric spatial memory	The ability to learn and remember location based on the relationship among objects or locations within the environment (Aguirre & D'Esposito, 1999).	Measured using the most direct route to the invisible target in the C-G Arena. Using the relationship between stationary cues rather than between self and cues to determine location.
Egocentric spatial memory	The ability to learn and remember location based on the relationship between objects or locations within the environment and oneself (Aguirre & D'Esposito, 1999).	Measured using NP tests, e. g. constructional praxis, Corsi Block-tapping, or by following specific paths in the C-G Arena.
Wayfinding	The ability to find one's way within the environment without getting lost (Davis et al., 2008).	Measured using C-G Arena, regardless of the frame of reference used to fine the invisible target.
Small-scale space	The process of being able to visualize an object or perceiving a single event, in a single time, at a single location but being separate from it (Siegel, Herman, Allen, & Kirasic, 1979)	Measured using paper and pencil tests which are in one field and can be solved using the relationship between self and object.
Large-scale space	Being within an event; an active participant, usually over the course of multiple time periods, multiple observations, and from different locations (Siegel et al., 1979).	Measured using a virtual reality or real world environment because multiple observations with novel starting points can be used to determine whether an individual can find his/her way.

Note. C-G = Computer-Generated; NP = Neuropsychological

Rich spatial representations of environments that are necessary for wayfinding have been proposed to be dependent on the hippocampus (Moscovitch et al., 2005). Further, certain aspects of memory, attention, and executive function such as the ability to remember relationships between cues; the ability to concentrate, maintain vigilance, respond to different elements, and shift focus as necessary; and the ability to engage in purposive, independent behavior may need to be intact for spatial memory and learning to occur (Lezak, Howieson, Loring, Hannany, & Fisher, 2004).

Gender and age are factors that have been demonstrated to influence spatial memory and learning. Researchers have shown gender can be associated with spatial memory performance, however, results were mixed, including: men performing better (Astur, Ortiz, & Sutherland, 1998; Canovas, Espinola, Iribarne, & Cimadevilla, 2008; Moffat, Zonderman, & Resnick, 2001; Rizk-Jackson et al., 2006; Tippett, et al., 2009), women performing better (Pressler, Subramanian et al., 2010), and mixed or no differences in spatial memory performance (Kober & Neuper, 2011; Spiers, Sakamoto, Elliott, & Baumann, 2008). Multiple researchers have demonstrated that younger participants exhibit significantly better spatial memory performance (Carelli et al., 2011; Gordon et al., 2008; Moffat, Zonderman, & Resnick, 2001; Moffat, Elkins, & Resnick, 2006; Newman & Kaszniak, 2000; Taillade et al., 2013). One study did not find differences in allocentric spatial memory performance between age groups (Iachini, Ruggiero, & Ruotolo, 2009), although egocentric spatial memory was better in younger age groups.

Socialization, physical activity, and cognitive activity are factors that have been shown to have a significant influence on spatial memory and learning in animal studies (Briones et al.,

2004; Briones et al., 2000; Cechetti et al., 2012; Zhu et al., 2011). These studies demonstrated that, when exposed to social conditions and physical and cognitive activities, rats with damage to the hippocampus were able to overcome the damage and their spatial memory and learning improved. While similar studies were not found in humans, HF patients may have a decreased ability to be involved in social, physical, and cognitive activities. This deprivation could result in a drastically smaller life and social space, leading to a shrinking world, creating a negative feedback loop.

The characteristics and patterns of spatial memory dysfunction in HF patients, such as losing everyday items, being late to appointments, or not being able to drive due to recurrent episodes of getting lost are not well understood. Research about how best to examine spatial memory performance in HF patients is limited and focused on egocentric spatial memory performance and samples have been relatively small (Alves et al., 2006; Athilingam et al., 2011; Beer et al., 2009; Callegari et al. 2002; Elkadi, Krum, & Storey, 2005; Riegel et al., 2002; Wolfe, Worrall-Carter, Foister, Keks, & Howe, 2006). Examinations of visuo-spatial abilities have used predominantly egocentric screening measures. When considering the measurement of allocentric spatial memory and learning, those screening measures may not be appropriate (Alves et al., 2006; Athilingam et al., 2011; Beer et al., 2009; Callegari et al. 2002; Elkadi et al., 2005; Pressler, Subramanian et al., 2010; Riegel et al., 2002; Trojano et al., 2003; Vogels, Oosterman, van Harten, Scheltens et al., 2007; Wolfe et al., 2006). No studies that specifically examined allocentric spatial memory in HF patients were found. The overall objective of this study was to describe and evaluate spatial memory and learning, specifically allocentric spatial memory, in HF patients. Specific aims and hypotheses were:

Aim 1: To compare allocentric spatial memory and learning of older (over 55 years of age) HF patients with healthy adults of similar age, using a computerized software program.

Hypothesis 1: Allocentric spatial memory is poorer in HF patients compared with age-matched healthy adults.

Hypothesis 2: Allocentric spatial learning is poorer in HF patients compared with age-matched healthy adults.

Aim 2: To determine the relationship between an allocentric virtual reality measure of spatial memory performance and egocentric paper and pencil measures of visuospatial memory performance.

Hypothesis 3: Allocentric spatial memory performance and egocentric visuospatial memory performance have a non-significant relationship.

Aim 3: To examine the influence of gender, group, perceived cognitive activity, and perceived functional capacity on spatial memory performance in older HF patients and age-matched healthy adults.

Overview of the Proposed Relationship Between HF and Spatial Memory Performance

Worsening HF severity, indicated by declining left ventricular ejection fraction (LVEF), worsening New York Heart Association (NYHA) classification and HF stage, and decreasing oxygenation was proposed to increase severity of hippocampal damage, thus worsening spatial memory performance. Further, it was proposed that the relationship was influenced by covariate factors (educational status, gender, and age). Environmental features (cognitive and physical activity levels) were hypothesized to moderate or mediate the influence of HF severity

on the hippocampus. Adults with spatial memory dysfunction may develop a decreased life space, social space and ultimately a shrinking world. Allocentric spatial memory was examined as the ability to locate a target in a computerized software program using the relationships among objects rather than the relationship between objects and self. The primary goal of this study was to synthesize the literature on spatial memory and learning in HF and to examine and compare spatial memory performance in adults with and without HF. The secondary goal was to determine if allocentric and egocentric spatial memory performance were correlated.

Theories About the Development of Spatial Memory and Learning

Cognitive map theory provides an explanation of how spatial memory functions. O'Keefe and Nadel (1978) developed their cognitive map theory to explain the relationship between the representation of space and memory, and the role of the hippocampus. The hippocampus is a cognitive mapping system which provides a flexible mental representation of the environment (O'Keefe & Nadel, 1978). A primary assumption of cognitive map theory is that the hippocampus is essential for the development of initial spatial learning, which is stored in cognitive maps in the hippocampus (Nadel, 1991). After cognitive maps are formed and information is consolidated into the maps, other areas of the brain (outside of the hippocampus) are responsible for storage (Nadel, 1991). A cognitive map enables spatial navigation to occur from any position in the environment, not based on one specific starting point (King, Burgess, Hartley, Vargha-Khadem, & O'Keefe, 2002). Cognitive maps allow novel shortcuts from different locations to a specific goal (King et al., 2002). According to O'Keefe (1991), in order for an individual to navigate, prediction of the goal requires direction and distance information within the cognitive map. Adults with hippocampal damage were

characterized as being unable to navigate using spatial imagery or a spatial cognitive map system, and unable to store long-term spatial memories (O'Keefe & Nadel, 1978). An important consideration of this representation is that when an individual has allocentric spatial memory dysfunction and a standard route (turn left at the corner, right at the next light) is not available, the individual may have serious difficulties getting to the intended location.

Standard consolidation theory is another major theory concerning the neural mechanism for spatial memory development in the hippocampus (Moscovitch, Nadel, Winocur, Gilboa, & Rosenbaum, 2006). During memory development, the neocortex, hippocampal complex, and medial temporal lobe integrate information by binding neurons together (Moscovitch, Rosenbaum et al., 2005). The bound neurons become a memory trace that undergoes short-term (synaptic) consolidation; this can take minutes to days to complete. After synaptic consolidation the memory trace goes through a period of prolonged (system) consolidation that can take from months to years to complete. During the prolonged consolidation phase the hippocampus/medial temporal lobes are responsible for access to the memory (Moscovitch, Rosenbaum et al., 2005).

Spatial memory performance may best be examined using a combination of the two theoretical models because both help to explain how an individual navigates in space. Cognitive map theory is the basis for the relationship of objects to other objects. As memory is accessed, the connection between goal points is strengthened and with time becomes consolidated. Once consolidated, storage may occur in structures of the brain other than the hippocampus. If hippocampal damage occurs due to chronic hypoperfusion, new cognitive maps cannot be formed. This may impact many areas of an individual's life because spatial memory needs may

change when an individual develops HF due to new clinic appointments, treatments, and medications. Memories that have undergone prolonged consolidation may not be affected by hippocampal damage due to their storage elsewhere in the brain.

Significance of the Research Study

According to the American Heart Association (AHA), in addition to the 5,100,000 with HF, 825,000 new patients are diagnosed each year in the U. S. (Go et al., 2014). Improved technology and medical therapies for cardiac illness have led to adults living through events (surgery, myocardial infarction) that previously would have resulted in death; due to this there are more HF patients and HF patients are living longer. The chronicity of HF may influence the development of long-term cerebral hypoperfusion and lead to right temporal lobe damage, specifically hippocampal damage. Differences have been demonstrated in spatial memory performance depending on the frame of reference (allocentric vs. egocentric) for patients with right temporal lobe damage (Maguire, Burke, Phillips, & Staunton, 1996; Spiers, Burgess, Maguire et al., 2001). Maguire, Burke and colleagues (1996) discussed a case of an eighteen year old man who had a right temporal lobe resection and tested in the unimpaired to above average range for several paper and pencil neuropsychological tests. However, he was grossly impaired on topographical orientation tasks using virtual reality. Further demonstrating this, Spiers, Burgess, Maguire and colleagues (2001) found significantly worse large-scale navigation using virtual reality in patients with right temporal lobectomy compared with neurologically normal adults. Standard paper and pencil neuropsychological test results did not demonstrate significant differences between the patients with right versus left lobectomy; however, testing was not completed in the neurologically normal participants.

These studies demonstrate an association between the right temporal lobe and allocentric spatial memory performance in humans. The association becomes less clear for HF and spatial memory performance due to other areas of the brain also being influenced by diminished cerebral blood flow. The other areas of the brain affected in HF patients may account for inconsistent differences found in paper and pencil measures of visuospatial memory. It may be that virtual reality computer programs specifically demonstrate impaired allocentric spatial memory performance due to right hippocampal damage and paper and pencil tests are demonstrating dysfunction of other brain structures.

Spatial memory performance is an essential ability for independent adults including those with HF. Severe HF frequently requires the use of multiple medications, exercise, dietary and fluid restrictions, and frequent medical appointments. In order to maintain independent functioning in daily life, the patient needs to have sufficient spatial memory, specifically, as well as other basic cognitive skills. Nurse scientists need to expand and extend the knowledge base of the factors that influence spatial memory performance in patients with HF. Determining factors that may be amenable to intervention is an important first step for future studies aimed at maintaining or improving spatial memory performance. Maintenance of spatial memory performance has the potential to help HF patients develop self-management skills in order to improve daily functional abilities.

Summary and Concluding Thoughts

Heart failure is a significant problem in the U. S. and the prevalence is increasing. There is a reasonable biological explanation for the presence of spatial memory dysfunction in HF patients. While it is clear that hippocampal damage influences spatial memory dysfunction, it is

not clear what other factors might influence spatial memory performance in HF patients. The relationship between the progression of HF and spatial memory performance is not clearly understood. Current knowledge about the characteristics and patterns (losing everyday items, not being able to drive, early behaviors to anticipate) of impaired spatial memory performance in HF patients is limited. Past studies had relatively small sample sizes and used egocentric screening measures, which may not be appropriate measures for allocentric spatial memory performance. Finally, it is unknown if spatial memory performance influences life space, social space, and a shrinking world or if a shrinking world due to decreasing life and social space influences spatial memory performance.

It is imperative to determine whether HF patients have spatial memory dysfunction and if so, which factors place them at risk for developing this dysfunction, and how best to identify these patients. If spatial memory can be identified as a basic cognitive domain of impairment in HF, then it could be hypothesized that in order to maintain functional abilities, adults with HF may need particularly explicit directions or cues to remember what needs to be done to effectively maintain self-care and daily functioning.

CHAPTER II

Review of the Literature

The goal of this chapter is to review the current knowledge about the relationship between HF and spatial memory performance. Literature was reviewed from October 1986 through February 2014. Key words included: spatial learning, spatial memory, cognition, small-scale, large-scale, egocentric, allocentric, navigation, and heart failure.

This chapter is organized into six main sections: 1) Theoretical perspectives of the relationship between HF and spatial memory performance; 2) Spatial memory and learning: what is known about spatial ability?; 3) Empirical knowledge of spatial ability: human brain structures and neuropsychology; 4) Potential predictors of spatial memory performance; 5) Gaps and limitations in the literature; and 6) Summary: Spatial memory and learning in HF patients.

Memory research has been said to have begun (Squire, 2009) with the description of a patient who had uncontrolled epilepsy that did not respond to medications, thus underwent bilateral-medial-temporal-lobe resection (Scoville & Milner, 1957). This initial brain lesion study led to an escalating number of studies that examined spatial memory and learning in animal models, which led to human studies of spatial memory performance.

Theoretical Perspectives of the Relationship Between HF and Spatial Memory Performance

Heart failure is a progressive disorder in which, due to a precipitating event, the heart is unable to pump blood effectively (Colucci & Braunwald, 2005). As a means to preserve

functional ability, HF causes activation of neurohormonal pathways (Laurent, 2005); this activation protects functional abilities in the short-term, but the compensatory mechanisms lead to damage of the myocardium with resultant impairment of functional ability (Colucci & Braunwald, 2005; Hunt et al., 2005). As a result of further myocardial damage and decreased pumping ability of the heart, due to these early compensatory mechanisms, oxygenation worsens and may influence the onset of cognitive dysfunction.

Cerebral hypoperfusion from decreased cardiac output is the most often cited etiology for the cognitive dysfunction found in HF (Bennett, Suave, & Shaw, 2005; Pressler, 2008; Pullicino & Hart, 2001; Siachos et al., 2005; Zuccala et al., 2005). Another frequently cited etiology is multiple cerebral emboli due to systolic dysfunction (Bennett et al., 2005; Pullicino & Hart, 2001; Siachos et al., 2005; Zuccala et al., 2005). During times of diminished arterial blood flow in healthy adults, due to autoregulation, blood is supplied to critical areas of the body, specifically the brain and heart. In HF patients, dysfunction of autoregulatory mechanisms within the brain may compound the diminished pumping ability of the heart and result in further cerebral hypoperfusion (Hoth et al., 2008; Zuccala et al., 2005). Animal studies (Briones et al., 2004; Briones et al., 2000) have shown a relationship between chronic cerebral hypoperfusion and spatial memory; however, little is known about the relationship between cerebral hypoperfusion in HF patients and spatial memory performance.

While little is known about the relationship between cerebral hypoperfusion in HF patients and spatial memory performance, a premise is that perceptually detailed representations, that are vividly recalled, result in accurate spatial memories (Moscovitch et al., 2005). Most likely an individual obtains knowledge about an environment, develops that

knowledge into a representation, then uses the representation to determine relationships among the locations within the environment to navigate. For example, an individual who can determine how to navigate from the local pharmacy to the local bakery, without prior experience in this particular route is using allocentric spatial memory. In contrast, an example of egocentric spatial memory is finding your way to a new gas station by following written instructions (go to the end of the street and turn right; drive three blocks then turn left; drive to the next corner).

Spatial memory can be examined using small-scale or large-scale space. Examples of small-scale space include remembering relationships between items on a sheet of paper, such as copying a drawing from the top of a sheet of paper to the bottom of the same sheet of paper, or repeating a particular order of tapping blocks on a board after observing the blocks being tapped. An individual who is completing a small-scale space measure would use an egocentric frame of reference because all of the objects can be visualized at the same time in one place (Maguire et al., 1996; Maguire, Burgess, & O'Keefe, 1999). Large-scale space is conceptually defined as occurring in the real world or in a simulated real-world environment (Maguire et al., 1996; Maguire, Burgess, & O'Keefe, 1999). Movement in large-scale space can be accomplished by an egocentric (following directions based on where the individual is located) or allocentric (using the relationships between objects within the environment) frame of reference.

A proposed relationship about the factors that predict an individual's ability to navigate within the environment was briefly discussed in Chapter I. A premise was proposed that the relationship between spatial memory and learning and HF was influenced by covariate factors

(educational status, gender, and age), which may provide a basis for predicting baseline ability. It was further proposed that environmental features (cognitive and social activity levels) may moderate or mediate the influence of HF on the hippocampus. Spatial memory performance was examined using a measure more applicable to an allocentric (able to find one's way in a virtual, computerized arena game using the relationship between objects) rather than an egocentric (the relationship between objects and oneself) frame of reference. The guiding philosophy to this research is that spatial memory dysfunction may lead to a decreased life space, social space and ultimately a shrinking world in which the individual finds it difficult to be independent. Navigation can be accomplished by either allocentric or egocentric spatial memory but this study focused specifically on examining allocentric spatial ability because it is dependent on hippocampal functioning.

Navigation, more specifically allocentric spatial memory, may have significant influence on the lives of those with HF by decreasing the individual's life space. Life space was defined by O'Connor, Edwards, Wadley and Crowe (2010) as the spatial extent of an individual's mobility, which could be an individual's home, block, or community. Dysfunctional allocentric spatial memory may influence an individual's life space negatively due to the inability to determine environmental relationships that, in turn, prevents unaccompanied trips out of the home. If an individual lives alone, the ability to get to clinic visits, the grocery store, or the drug store may be severely affected, further influencing health status.

Furthermore, an individual's social space may be influenced by the functionality of allocentric spatial memory. Social space is a socially supported system, located within a geographic area, in which attitudes and beliefs are uniform and stable and knowledge and

meaning are shared among the inhabitants (Liu & Sibley, 2004). As allocentric spatial memory worsens the individual may experience a decrease in social space due to limitations on his or her ability to interact thus losing a sense of cohesion with others in the community.

Ultimately, impaired allocentric spatial memory may lead to a shrinking of the individual's world. A shrinking world entails having a smaller geographical area in which the individual is active and is experienced as a loss of control and decreased independence (Duggan, Blackman, Martyn, & Schaik, 2008). The model that Duggan et al. (2008) developed demonstrated that disorientation, confusion, and memory loss led to a loss of confidence, anxiety, and fear of getting lost, resulting in a shrinking world. Physical and emotional well-being was maintained by being active in the environment and by being involved in social interactions, which facilitate a general sense of exploration (Duggan et al., 2008). Decreased life space, social space, and a shrinking world make it difficult for an individual to complete independent self-care activities that require travel outside the home.

Spatial Memory and Learning: What is Known About Spatial Ability?

Empirical Support in Animal Models

Because the hippocampus is susceptible to ischemia (inadequate blood supply), it is often studied in relationship to conditions affecting blood flow to the brain. In animal studies, the Cornu Ammonis sector 1 (CA1) region of the hippocampus has been shown to be the most vulnerable area in terms of injury due to ischemia (Duvernoy, 2005; Sadowski et al., 1999; Vallet & Charpiot, 1994). During short periods of ischemia, neurons in the CA1 area were found to be susceptible to damage; while the neurons in the Cornu Ammonis sector 3 (CA3) and dentate gyrus regions were resistant to injury (Sadowski et al., 1999; Vallet & Charpiot, 1994).

In rats exposed to ischemic conditions, compared with nonexposed rats, no decrease in CA3 and dentate gyrus neurons was found at 3 days, however, a significant decrease of the CA3 and dentate gyrus neurons was found at 14 days (Sadowski et al., 1999).

Authors of multiple animal studies have examined spatial memory under the condition of transient global cerebral ischemia; however this was not the focus of this review because the cerebral hypoperfusion of sudden onset may be different from the more gradual onset of cerebral hypoperfusion in HF. Models of chronic cerebral hypoperfusion have been used to evaluate the relationship between hippocampal damage and spatial memory performance in rats (Cechetti et al., 2012; De Jong et al., 1999; Hai et al., 2009; Sekhon, Morgan, Spence, & Weber, 1994; Sivilia, Giuliani, Del Vecchio, Giardino, & Calza, 2008; Sun et al., 2010; Thong, Chompoopong, Tantisira, & Tilokskulchai, 2013; Vicente et al., 2009; Wang et al., 2010; Zhu et al., 2011; see table 2.1). One or two vessel (common carotid artery) occlusion was used to simulate non-ischemic, decreased cerebral blood flow in all but two of these studies either. Two studies (Hai et al., 2009; Sekhon et al., 1994) used an arteriovenous fistula to produce chronic cerebral hypoperfusion in a rat model.

Chronic cerebral hypoperfusion was related to significant pathological changes in the hippocampus and in spatial memory performance of rat models for all studies identified in this review (see table 2.1). Several researchers found significantly worse neurodegeneration in study rats compared with control rats in the CA1 area of the hippocampus during histological exam up to 3 months after induced chronic cerebral hypoperfusion (Cechetti et al., 2012; Hai et al., 2009; Thong et al., 2013; Vicente et al., 2009). Long-term potentiation (LTP), a cellular mechanism essential for consolidation of learning and memory, was found to be significantly

lower in study rats compared with control rats following chronic cerebral hypoperfusion (Hai et al., 2009; Sekhon et al., 1994). Wang and colleagues (2010) found significantly less synaptic density of CA1 neurons and a significantly increased accumulation of oligomeric amyloid-β in the hippocampus of hypoperfused rats. Finally, De Jong and colleagues (1999) demonstrated decreased capillary integrity in the CA1 area of the hippocampus, which was correlated with spatial memory performance on the Morris water maze. Poorer performance on the Morris water maze task after induced chronic cerebral hypoperfusion was demonstrated in multiple studies that examined allocentric spatial memory and learning (Cechetti et al., 2012; Hai et al., 2009; Sun et al., 2010; Thong et al., 2013; Vicente et al., 2009; Wang et al., 2010; Zhu et al., 2011).

Table 2.1 Studies That Examined the Effects of Chronic Cerebral Hypoperfusion on Spatial Memory and Learning in a Rat Model

Study	Design	Sample	Measures	Results
Cechetti et al., 2012	Experimental design; 2-vessel occlusion and sham surgery	66 male Wistar rats randomized to experimental (n = 37) or control (n = 29) groups	Morris water maze, histology	Experimental group significantly worse spatial memory than control at 3 and 6 months of testing. CA1 neurodegeneration significantly worse in experimental compared with control rats at 7 days and 3 months
DeJong et al., 1999	Experimental design; 2-vessel occlusion	12 male Wistar rats randomized to experimental (n = 7) or control (n = 5) groups	Morris water maze, histology	Time to platform significantly quicker in control rats. Significantly more degenerative changes in CA1 capillaries of hypoperfused rats vs. controls
Hai et al., 2009	Experimental design; Arteriovenous fistula	12 Sprague-Dawley rats randomized to experimental or control groups	Morris water maze, histology	Spatial memory and learning significantly worse in hypoperfused vs. control rats. Significantly worse neurodegeneration in CA1 area of hypoperfused rats.

Study	Design	Sample	Measures	Results
Sekhon et al., 1994	Experimental design; Arteriovenous fistula	30 male Sprague-Dawley rats randomized to experimental (n = 13) or control (n = 17) groups	Histology	LTP of CA1 hippocampal neurons was significantly worse in hypoperfused than control rats
Sivilia et al., 2008	Experimental design; 2-vessel occlusion	24 male Sprague-Dawley Albino rats randomized to experimental (n = 15) or control (n = 9) groups	Histology	Proliferation and neurogenesis of hippocampal cells was significantly increased in young but not middle aged animals compared with controls.
Sun et al., 2010	Experimental design; 2-vessel occlusion and sham surgery	Rats randomized to four groups: 2-vessel occlusion EE or standard; sham surgery EE or standard	Morris water maze; neurochemical hippocampal levels	Rats with 2-vessel occlusion significantly worse than sham rats on Morris water maze performance. Rats housed in enriched environment experienced reversal of impaired water maze performance
Thong et al., 2013	Experimental design; right common carotid artery occlusion	20 Sprague-Dawley rats equally randomized to experimental or control groups	Radial arm water maze; Morris water maze; histology	Model rats were significantly worse than control rats at six days and 2 months. Significant differences were not found at 4 months.

Study	Design	Sample	Measures	Results
Vicente et al., 2009	Experimental design; 2-vessel occlusion and sham surgery	16 male Wistar rats equally randomized to experimental or control groups	Morris water maze; histology	Reference and working spatial memory significantly worse in experimental animals.
Wang et al., 2010	Experimental design; 2-vessel occlusion and sham surgery	96 male Sprague-Dawley rats randomized to experimental (4 groups of 12) or control (4 groups of 12)	Morris water maze; histology	Hypoperfused rats had significantly impaired spatial memory performance (at 30, 90, & 120 days) compared with sham rats
Zhu et al., 2011	2-vessel occlusion and sham surgery	64 male Wistar rats randomized to 4 groups: sham, sham + EE, model, model + EE	Morris water maze; histology	Hypoperfused rats had significantly worse spatial memory and learning than hypoperfused + EE or Sham with or without EE. Hypoperfusion impaired LTP and EE reversed the impairment

Note. CA1 = Cornu Ammonis 1; CA3 = Cornu Ammonis 3; EE = enriched environment; EC = complex environment; LTP = long-term potentiation; IV = Independent variable; SC = social condition

These studies support the existence of a relationship between chronic cerebral hypoperfusion and spatial memory dysfunction, most likely through damage to the CA1 area of the hippocampus and due to decreased LTP with resultant difficulties in learning and memory. While it cannot be determined at this time if these animal models of chronic cerebral hypoperfusion are representative of what happens in adults with HF, they provide a basis for further study.

Empirical Knowledge of Spatial Ability: Human Brain Structures and Neuropsychology

Spatial Ability and Brain Lesions

Although allocentric spatial memory performance has not been specifically examined in HF patients, it has been studied among healthy and brain lesioned adults (see table 2.2). One of the first known studies of spatial memory in humans was on an individual who, due to an incapacitating seizure disorder, had undergone a radical-bilateral-medial temporal-lobe resection (Scoville & Milner, 1957). Following the procedure, the severity and frequency of the seizures decreased enough to allow the patient to function in his daily activities but he had severe deficits in his ability to find his way to new locations or to remember where items were placed. A second patient who had a similar operation and was who was unable to find his way to his hospital room was also described. Scoville and Milner conducted intelligence quotient (IQ) tests before and after the procedures; neither of the patients had significantly different post-procedure IQ test scores compared with pre-procedure scores. Six other patients were described who had impaired memory without significant effects on IQ after bilateral removal of the hippocampus; however spatial memory and learning were not discussed in these patients.

Researchers in two other studies (Spiers, Burgess, Maguire et al., 2001; Zola-Morgan, Squire, & Amaral, 1986) examined spatial memory after hippocampal damage and found deficits. Navigation and map drawing were significantly worse in a group of patients with right temporal lobe damage compared with a control group. Patients with left hippocampal damage were worse than controls but the difference did not reach statistical significance (Spiers, Burgess, Maguire, et al., 2001). Zola-Morgan and colleagues (1986) completed a case study of a man who experienced a bilateral lesion to the CA1 area of the hippocampus. Until his death almost five years after initial testing the patient's performance on numerous neuropsychological tests, with the exception of memory tests including spatial memory, was normal (Zola-Morgan et al., 1986).

Table 2.2 Studies of Spatial Memory in Adults with Brain Lesions

Study	Design	Sample	Measures	Results
Scoville and Milner, 1957	Descriptive	10 patients with bilateral medial temporal-lobe resection	Wechsler Intelligence and Memory Quotients; qualitative descriptions of abilities	3 had severe memory defect; 5 had moderate memory defect and 2 had no memory defect; 1 patient unable to find his way to new places or remember where objects belong
Spiers, Burgess, Maguire et al., 2001	Comparative	17 right and 13 left temporal lobectomy patients, 16 healthy adults	Rey-Osterrieth Complex Figure, virtual reality town navigation, computer map drawing	Significantly worse accuracy and map drawing than healthy adults
Zola-Morgan et al., 1986	Descriptive	Case study of 52 year old male with hippocampal damage	Rey-Osterreith Complex Figure copy and recall	Severely impaired score for figure copy recall

Neuroimaging and Spatial Ability

Allocentric spatial memory has been studied using imaging techniques including functional magnetic resonance imaging (MRI) and positron emission tomography (PET; see table 2.3). Many of the imaging studies have used virtual reality computer programs, relatively recently developed, to specifically examine allocentric spatial memory in healthy and hippocampal-damaged adults. Although the studies in table 2.3 were completed in healthy adults, they lend support to the premise that damage to the hippocampus may result in spatial memory and learning dysfunction.

Brain activity was examined in healthy adults using fMRI while navigating in computer generated virtual reality environments (Bohbot, Lerch, Thorndycraft, Iaria, & Zijdenbos, 2007; Iaria et al., 2003; Shipman & Astur, 2008; Suthana et al., 2009). Significantly higher gray matter density was found in the hippocampus of those who used an allocentric rather than an egocentric frame of reference to navigate (Bohbot, et al., 2007; Iaria et al., 2003; Shipman & Astur, 2008; Suthana et al., 2009); further, gray matter density in the hippocampus was correlated with probe errors (Bohbot et al., 2007); these findings suggest that the hippocampus is responsible for allocentric navigation. Further supporting hippocampal dependent allocentric navigation, significant increases in activity were found in the right hippocampus during allocentric spatial navigation; this was not the case, when adults used a nonspatial means of navigating the environment (Iaria et al., 2003). Shipman and Astur (2008) found that cell activation occurred in the right hippocampus during location of a goal, but not during movement to the goal; this indicates that hippocampal cells are activated by goal determination rather than movement to the goal. Allocentric spatial memory as demonstrated

by learning goal locations from different starting points had significantly more activity in the right CA1 subregion of the hippocampus compared with an egocentric (one starting point) frame of reference (Suthana et al., 2009), further supporting right hippocampal involvement in allocentric navigation.

Ekstrom and colleagues (2003) examined neurons in the brain during a taxi driver virtual-reality game using implanted electrodes and electroencephalogram to assess spatial navigation. Neurons fired in the hippocampus on arrival at specific spatial locations, while neurons in the parahippocampal region fired during visualization of cues indicating that the hippocampus is involved in the encoding of the location (place-responsive cells) while the parahippocampus is involved in the recognition of objects (view-responsive cells; Ekstrom et al., 2003). The relationship between allocentric spatial memory and brain regions was examined and it was determined that participants with right temporal lobectomy had significantly worse large-scale navigation accuracy and map drawing than a neurally intact group (Spiers, Burgess, Maguire et al., 2001). Navigation was worse in the right-temporal-lobectomy patients when compared with the left-temporal-lobectomy patients; however, it did not reach the level of significance. Importantly, standard small-scale memory tests were not significantly different except in the Warrington Recognition Memory Test for Faces indicating damage limited to the hippocampus may result in allocentric but not egocentric spatial memory dysfunction (Spiers, Burgess, Maguire et al., 2001).

Table 2.3 Neuroimaging Studies: Adults Without HF

Study	Design	Sample	Measures	Results
Bohbot et al., 2007	Comparative	30 healthy adults 17 men, 13 women	VR maze fMRI	Significantly more hippocampal gray matter density in spatial versus response learners
Ekstrom et al., 2003	Exploratory	7 patients with epilepsy, 5 men, 2 women	VR taxi driver game	Cells that respond to specific spatial locations are primarily in the hippocampus; parahippocampus is responsible for landmarks.
Iaria et al., 2003	Exploratory	50 healthy adults; 25 men, 25 women	fMRI	Significantly more activity in hippocampus during spatial navigation versus non-spatial navigation

Study	Design	Sample	Measures	Results
Maguire, Frackowiak, & Frith, 1997	Factorial	11 London taxi drivers all men	PET scan, demographics, real world route recall	Right hippocampal activity increased with route recall but not recall of landmarks.
Maguire, Frackowiak, & Frith, 1996	Exploratory	8 healthy adults, all men	PET scan	Significantly higher right hippocampal and right and left hippocampal gyrus activity during spatial versus non-spatial navigational viewing
Shipman & Astur, 2008	Experimental	28 healthy young participants (mean age 21.4; 14 men, 14 women)	VR water maze, fMRI	Right hippocampal activity increased during initiation of hidden trials, hippocampal activity increased during fixation on a crosshair

Study	Design	Sample	Measures	Results
Suthana et al., 2009	Exploratory	18 healthy adults (20-31 years of age)	fMRI during VR learning	Significantly more hippocampal CA1 activity during allocentric spatial memory learning

Note. CA1 = Cornu Ammonis 1; fMRI = functional magnetic resonance imaging; PET = positron emission tomography; VR = Virtual Reality

This literature supports a relationship between the hippocampus, in particular the right hippocampus, and spatial memory and learning. It should be noted that, however, as is common in imaging research these studies did not have large sample sizes.

Neuroimaging and Pathology in HF patients

Past cognitive research related to HF has established that cognitive deficits are significantly worse in HF patients as compared with healthy adults (see table 2.4). Neuroimaging studies have identified potential etiologies underlying cognitive impairment in HF, including lower cerebral blood flow and more brain pathology in HF patients compared with healthy adults. Specifically, HF patients were found to have: lower cerebral blood flow (Choi et al., 2006; Gruhn et al., 2001); decreased mammillary body volume and increased fornix fiber injury (Kumar et al., 2009); lower cerebral blood flow velocity and pulsatility index (Vogels, Oosterman, Laman et al., 2008); decreased gray matter in the parahippocampal gyrus, primarily on the right (Woo, Macey, Fonarow, Hamilton, & Harper, 2003); and a significantly smaller right posterior hippocampus (Woo et al., 2009). Significant correlations were found between cerebral blood flow and NYHA classification and between cerebral blood flow and disease duration (Choi et al., 2006). New York Heart Association classification was identified as an independent predictor for cerebral blood flow by multiple linear regression (Choi et al., 2006).

Table 2.4 Imaging Studies of Pathology in HF Patients

Study	Design	Sample	Measures	Results
Choi et al., 2006	Comparative, correlational	52 HF (79% men, mean age 41 years), 10 healthy volunteers (70% men, mean age 39 years)	Radionuclide angiography	NYHA was significantly associated with cerebral blood flow
Gruhn et al., 2001	comparative	12 HF (92% men, mean age 52 years), 12 healthy adults (92% men, mean age 47 years)	SPECT	Cerebral blood flow volume was significantly lower in HF compared with healthy adults
Kumar et al., 2009	comparative	17 HF (71% men, mean age 54.4 years), 50 healthy adults (58% men, mean age 50.6 years)	3 Tesla, T1 weighted MRI, demographics	Mammillary body volume and fornix fibers were significantly lower in HF patients vs. healthy adults.
Vogels, Oosterman, van Harten, Gouw et al., 2007	Correlational	58 HF patients (74% men, mean age 68.7 years)	MRI; fragmented line drawing, object recognition	Worse cognitive performance was correlated with MTA

Study	Design	Sample	Measures	Results
Vogels et al., 2008	Comparative, correlational	43 HF (81% men, mean age 68.0 years); 33 non-HF, cardiac participants (79% men, mean age 67.8 years); 22 healthy adults (55% men, mean age 64.1 years)	Transcranial Doppler ultrasonography; fragmented line drawing, object recognition	Blood flow not correlated to visuospatial scores; HF patients had significantly lower visuospatial scores than cardiac and healthy adults
Woo et al., 2009	Comparative design	13 HF (69% men, mean age 54.6 years); 49 healthy adults (59% men, mean age 50.6 years)	3 Tesla, T2 weighted MRI; demographics	Significantly greater tissue injury and damage in the hippocampus of HF patients compared with healthy adults
Woo et al., 2003	Comparative	9 HF (67% men, mean age 51 years); 27 healthy adults (81% men, mean age 46 years)	Structural MRI	HF patients had significantly more gray matter loss in parahippocampal gyrus than healthy controls

Note. HF = Heart Failure; MRI = functional magnetic resonance imaging; MTA = medial temporal lobe atrophy; NYHA = New York Heart Association; SPECT = single-photon emission computed tomography

The studies in table 2.4 connect the different aspects of diminished cerebral blood flow in HF patients, damage to brain structures responsible for spatial ability, and the development of cognitive dysfunction, specifically, visuospatial ability. Although neuropsychological testing was not performed in most of these studies, the studies support the association of diminished cerebral blood flow in HF patients with subsequent changes in brain pathophysiology. As HF severity worsens, cerebral blood flow may further contribute hippocampal damage and the resulting spatial memory dysfunction. The above studies support the hypothesis that the cerebral hypoperfusion present in HF is associated with hippocampal damage. The resultant damage to the hippocampus should then be associated with dysfunctional spatial memory in HF patients, presenting as errors in navigation tasks. A limitation of the reviewed literature on imaging in HF patients is that these studies had relatively small sample sizes with only two studies (Choi et al., 2006; Vogels, Oosterman, van Harten, Gouw et al., 2007) having more than 50 HF patients. The majority of the studies (Gruhn et al., 2001; Kumar et al, 2009; Woo et al., 2009; Woo et al., 2003) had fewer than 20 HF patients. Another issue was that all of these studies had a greater percentage of men than women with all but two (Woo et al., 2009; Woo et al., 2003) having more than 70% men. The consistent findings in these neuroimaging studies completed in HF patients, even with small numbers of enrolled participants provides more support to the hypothesis that spatial memory is a concern in HF patients.

Visuospatial Memory and HF patients

Visuospatial abilities have been examined in multiple studies, using neuropsychological tests, as part of a cognitive profile in HF patients (see table 2.5). Visuospatial abilities were examined using various measures including the: Block Design test, Brief Visuospatial Memory

Test – Revised (BVMT), praxis subscale of the Cambridge Mental Disorders of the Elderly Examination (CAMCOG), Clock Drawing Test (CDT), Corsi Block-tapping test, Rey Complex Figure Test, Figure Copy Test of the Consortium to Establish a Registry for Alzheimer's Disease (CERAD) battery, Raven's Matrices, fragmented line drawing, and Repeatable Battery for Assessment of Neuropsychological Status (RBANS) – visuospatial constructional index (Alves et al., 2006; Beer et al., 2009; Callegari, et al., 2002; Elkadi et al., 2005; Pressler, Subramanian et al., 2010; Riegel et al., 2002; Trojano et al., 2003; Vogels, Oosterman, van Harten, Sheltens et al., 2007; Wolfe et al., 2006). Authors in six of these eight studies found HF patients had significantly worse visuospatial abilities than healthy adults (Alves et al., 2006; Beer et al., 2009; Callegari, et al., 2002; Elkadi et al., 2005; Vogels, Oosterman, van Harten, Sheltens et al., 2007; Wolfe et al., 2006). Differences were not significant in two of the eight studies (Pressler, Subramanian et al., 2010; Trojano et al., 2003).

Most of the investigators matched or adjusted for age, gender, and education (Alves et al., 2006; Beer et al., 2009; Callegari, et al., 2002; Pressler, Subramanian et al., 2010, Riegel et al., 2007) or for age and education (Elkadi et al., 2005; Trojano et al., 2003; Vogels, Oosterman, van Harten, Sheltens et al., 2007). Investigators in one study (Wolfe et al., 2006) used age-adjusted normative scores for comparison, however they also examined premorbid intellect to determine if patients had changed significantly from their level prior to being diagnosed with HF. Beer and colleagues (2009) examined brain regions of HF patients and healthy adults using MRI; HF patients had significantly worse right-medial-temporal-lobe atrophy when compared with healthy adults.

Table 2.5 Studies of Visuospatial Memory in HF: Neuropsychological Testing

Study	Design	Sample	Measures	Results
Alves et al., 2006	Comparative, descriptive	34 HF patients (50% men, mean age 74.9 years), 18 HA participants (33% men, mean age 72.8 years)	Praxis subscale of CAMCOG	Poorer visuospatial abilities in HF patients compared with healthy adults
Beer et al., 2009	Descriptive, correlational	31 HF patients (83.9% men, mean age 54.3 years), 24 HA (83.3% men, mean age 56.1 years)	BVMT, Block Design test, MRI	BVMT and Block Design total and delayed scores and temporal lobe atrophy significantly worse in HF versus healthy adults
Callegari et al., 2002	Comparative	64 HF patients (all men, mean age 51.8)	CBT, RPM	Significantly worse spatial memory per CBT and RPM in HF patients versus normative data for test
Elkadi et al., 2005	Comparative	44 HF patients (mean age 56.3 years), 22 age and education matched HA (mean age 54.8 years); gender not stated	Rey Complex Figure Test	Visuospatial memory - immediate scores significantly worse in HF versus healthy adults

Study	Design	Sample	Measures	Results
Pressler, Subramanian et al., 2010	Comparative	249 HF (63% men, mean age 62.9 years), 102 MC (27% men, mean age 63 years), 63 HA (29% men, mean age 53.3 years)	Figure Copy and Figure Memory Recall	No significant difference in the 3 groups (p = .700 Figure Copy; .770 Recall
Riegel et al., 2002	Descriptive, correlational	42 class I, II, III, & IV HF patients (50% men, mean age 74.7 years)	CDT	CDT found cognitive dysfunction in 50% of patients identified as impaired.
Trojano et al., 2003	Comparative	159 class III & IV HF (48% men, mean age 76.8 years), 149 class II HF (50% men, mean age 74.7 years), 207 non-HF patients (43% men, mean age 73.7 years)	Raven Coloured Progressive Matrices, CBT	No significant differences in visuospatial scores among the three groups
Vogels, Oosterman, van Harten, Scheltens et al., 2007	Comparative	62 HF (74% men, mean age 69.2 years), 53 cardiac controls (70% men, mean age 68.6 years), 42 HA (55% men, mean age 67.2 years)	Fragmented line drawing	Visuospatial function significantly worse in HF patients versus healthy controls

Study	Design	Sample	Measures	Results
Wolfe et al., 2006	Comparative	38 HF patients (76% men, mean age 64 years)	RBANS, visuospatial constructional subtest	Visuospatial skills significantly worse in HF patients than age expected published norms

Note. BDAE = Boston Diagnostic Aphasia Examination; BVMT = Brief Visuospatial Memory Test-Revised; CAMCOG = Cambridge Cognition examination; CBT = Corsi Block-tapping; CDT = Clock Drawing Test; HA = healthy adults; HF = heart failure; MC = medical control participants; MRI = magnetic resonance imaging; RBANS = Repeatable Battery for Assessment of Neuropsychological Status; RPM = Raven Progressive Matrices

Spatial memory performance dysfunction was demonstrated in previous studies, a number of factors were responsible for the mixed results (see table 2.5). Different neuropsychological tests were used to measure spatial memory performance, making it difficult to compare the study results. Some of the studies did not control for factors that have been shown to affect neuropsychological test scores (age, gender, education). Further, small-scale egocentric tasks, which may not be indicators of allocentric spatial memory were used to measure spatial abilities in the majority of the studies (except Pressler, Subramanian et al., 2010; Wolfe et al., 2006). The majority of these studies included mainly men and had small sample sizes (except Pressler, Subramanian et al., 2010; Trojano et al., 2003) making it difficult to generalize the findings.

Importantly, a study by Pressler, Kim, Riley, Ronis and Gradus-Pizlo (2010) examined explanatory factors for mortality in HF patients and found a significant relationship between visuospatial memory and mortality. Visuospatial memory scores were significantly better in patients who were still living one year following the initial assessment compared with the scores of those who had died.

Characteristics and patterns of spatial memory dysfunction in the HF population have been studied minimally and it is not yet clear how best to measure it or what explains spatial memory. Multiple studies have shown a 23-50% occurrence of cognitive dysfunction, including memory, in HF patients however spatial memory was not the focus (Almeida & Flicker, 2001; Bennett & Suave, 2003; Callegari et al., 2002; Pressler, 2008; Pressler, Subramanian et al., 2010; Vogels, Oosterman, van Harten, Scheltens et al., 2007; Vogels, Scheltens, Schroeder-Tanka, & Weinstein, 2007).

Two studies (Bennett, Cordes, Westmoreland, Castro, & Donnelly, 2000; Clark & McDougall, 2006) were found in which the ability to navigate was identified through patient or family report in HF patients. Researchers from these studies examined HF patients using a qualitative approach (see table 2.6). During discussion with patients it was noted that many of the patients had problems with navigation and with getting lost. While these studies did not specifically test navigation and had small sample sizes, patients and family members noted that problems with navigation existed and in some cases it was left up to the spouse to drive.

Table 2.6 Spatial Memory and HF: Qualitative Studies

Study	Design	Sample	Measures	Results
Bennett et al., 2000	Focus group methodology	23 HF (70% men, mean age 60 years) and 18 family members (6% men) of HF patients; family members included wives, siblings, children, 1 grandson; ages not identified	Focus group interviews with patients and family members	Memory and navigation dysfunction perceived to be worse by family members than by patients.
Clark & McDougall, 2006	Descriptive	11 HF patients, (73% men, mean age 74 years)	Audio taped interviews with patients	Verbalized difficulties with ability to remember directions

Note. HF = heart failure

Potential Predictors of Spatial Memory Performance

The majority of what is known about spatial memory has been learned through animal studies, early human brain lesion studies, and most recently in studies using computer based software. Factors including age, gender, education, and cognitive, social, and physical activity levels have been shown to be associated with spatial memory in studies completed in animal models of cerebral hypoperfusion (acute and chronic) and in healthy adults.

Gender and Allocentric Spatial Memory

Spatial ability was significantly different between men and women in multiple studies (Astur et al., 1998; Canovas et al., 2008; Moffat et al., 1998; Rizk-Jackson et al., 2006; Tippett et al., 2009), each indicating that men have better accuracy and speed to the target or goal during virtual reality tests to assess large-scale spatial memory (see table 2.7). However, researchers in one study (Spiers, Sakamoto, Elliott, & Baumann, 2008) found women did better on spatial memory tasks and in another study (Kober & Neuper, 2011) found no difference between men and women.

The virtual reality programs included a virtual Morris water task in which college students needed to find an invisible target (Astur et al., 1998); the Boxes Room in which college students needed to obtain a set number of rewards hidden in boxes (Canovas et al., 2008); a virtual reality maze in which healthy adults needed to find the shortest path between landmarks (Kober & Neuper, 2011); a virtual reality maze in which college students needed to find the exit door (Moffat et al., 1998); a virtual reality water maze called Memory Island in which college students needed to find a hidden target in the water that surrounded the island using a head mounted display system (Rizk-Jackson et al., 2006); a virtual reality grocery store

in which healthy adults needed to recall objects and map object location (Spiers et al., 2008); and finally, a virtual reality maze of a city in which healthy adults needed to determine navigational skills (Tippett et al., 2009). Allocentric spatial memory has been measured by how quickly a hidden platform or target is found, the number of errors in the route, the length of the route, and by how much time is spent in the target quadrant, after the target was removed. A combination of these measures was used in the reviewed studies (see table 2.7).

Table 2.7 Studies on Gender and Spatial Memory Performance

Study	Design	Sample	Measures	Results
Astur et al., 1998	Experimental	40 undergraduate college students (50% men, mean age not reported)	VR Morris water maze	Men found platform significantly quicker, less swimming error, more probe crossings
Canovas et al., 2008	Evaluative	63 undergraduate college students (48% men, mean age 22.2 years; women mean age 20.7 years)	VR Boxes Room	Men significantly faster and more accurate than women in VR spatial memory tasks.
Kober & Neuper, 2011	Comparative	27 young adults (48% men, mean age 25.5 years, 52% women, mean age 23.8 years)	Theta oscillations per electroencephalo-gram; VR maze; spatial recognition task	Hippocampal activity increased more from baseline in women than in men during landmark processing; no difference in spatial navigation between men and women

Study	Design	Sample	Measures	Results
Moffat et al., 1998	Comparative	74 undergrad college students (54% men mean age 20.3 years; 46% women, mean age 19.5 years)	VR maze, small-scale and verbal NP tests	Men significantly better on paper/pencil spatial tests and VR maze tests
Rizk-Jackson et al., 2006	Comparative	27 community college students (52% men, mean age 29.1 years; women mean age 31.5); 24 University students (58% men, mean age 30.5 years)	Facial/object recognition, VR-Memory Island	Facial/object recognition had no effect of gender, no difference in time to visible target; men significantly quicker to hidden target, more accurate and more success finding the target

Study	Design	Sample	Measures	Results
Spiers et al., 2008	Comparative	40 young healthy adults (50% men, mean age 20.4 years) age and education matched	VR Spatial Object-Location Test, mental rotation, 2D object-location memory tasks	Women had significantly better object-location in the 3D spatial VR environment and the 2D memory tasks; men had significantly better mental rotation abilities
Tippett et al., 2009	Comparative	24 healthy older adults (50% men, mean age 69.7 years; women mean age 69.1 years)	VR city navigation task, Groton Maze Learning Test, NP tests	Men had significantly better spatial memory performance than women including less deviation from the correct path, efficiency scores and peak performance.

Note. NP = neuropsychological tests; VR = Virtual Reality

In five of the seven studies (Astur et al., 1998; Canovas et al., 2008; Moffat et al., 1998; Rizk-Jackson et al., 2006; Tippett et al., 2009), men were significantly faster at finding the target, used a shorter path, had fewer route errors, and/or spent significantly more time in the target quadrant after the target was removed. These differences were not found in the trials where the target was visible; this supports spatial ability differences were present between men and women and these differences were not due to the ability to use the device to navigate within the virtual reality environment. These five studies (Astur et al., 1998; Canovas et al., 2008; Moffat et al., 1998; Rizk-Jackson et al., 2006; Tippett et al., 2009) were not conducted with HF patients, had small sample sizes, and were completed with adults who were younger than typical HF patients. Results did indicate that differences in spatial memory performance between young healthy men and women existed, and as such, gender was examined as a variable.

Age and Spatial Memory Performance

Age has been reported in numerous studies to affect cognitive performance including spatial memory (see table 2.8). In six studies, investigators used virtual reality environments including a virtual town in which healthy adults were taxi drivers (Iaria, Ruggiero, & Ruotolo, 2009), the Computer-Generated Arena (CG-A) similar to the Morris Water Maze task (Davis et al., 2009; Laurance et al., 2002), and a maze of halls and doors with one exit door that must be found (Moffat et al., 2001). Another group of investigators (Newman & Kaszniak, 2000) developed a spatial memory test conducted in a tent-like enclosure in which a pole needed to be placed in a certain position. Significantly better learning and probe scores were found in younger adults compared with the older adults in all but one of the studies discussed in table

2.8 (Iachini et al., 2009). Age differences in navigational behavior were supported in these studies by older age adults taking longer to find the goal and making more errors in their paths to the goal.

Table 2.8 Studies on Age and Spatial Memory Performance

Study	Design	Sample	Measures	Results
Carelli et al., 2011	Comparative	8 patients (aged from 42 to 71 years; 63% men) with focal brain lesions, 40 HA (aged from 40 to71 years; 38% men)	VR-Maze test, paper and pencil version of VR-Maze test, NP tests including spatial ability (Rey's complex figure copy, Benton's line orientation test, Elithorn's Perceptual Maze test)	Older HA had worse VR task performance with significantly longer times to complete mazes
Gordon et al., 2008	Comparative	60 HA 20 young (aged from 20 to 28 years; 50% men), 40 elderly (aged from 65 to 81 years; 43% men)	WAIS-R box completion, RPM	MTL atrophy significantly worse in elderly versus younger participants. RPM and boxes scores significantly worse in elderly versus younger groups

Study	Design	Sample	Measures	Results
Iachini et al., 2009	Comparative	140 HA Divided into 7 groups (20-29; 30-39; 40-49; 50-59; 60-69; 70-79; 80-89 years of age; 50% men)	Table-top object relationships	No significant changes in allocentric spatial memory per age bracket
Moffat et al., 2001	Comparative	24 young adults (aged from 22 to 44 years; 50% men) 43 middle aged adults (aged from 45 to 65 years; 49% men); 46 older adults (aged over 65 years; 72% men)	VR maze, demographics, other NP tests	Older participants: significantly more errors in navigation, longer to solve, longer distance traveled; positively correlated with mental rotation and visual memory.
Newman et al., 2000	Comparative	16 younger adults (aged from 18 to 30 years; 56% men); 17 healthy older adults (aged from 61 to 82 years; 41% men)	Real world spatial memory testing enclosure	Younger adults had significantly better scores (time to target, accuracy)

Study	Design	Sample	Measures	Results
Taillade et al., 2013	Comparative	23 young adults (mean age 22.9 years), 24 older adults (mean age 64.8 years); authors did not report gender or age ranges	Spatial Orientation questionnaire, VR spatial memory and learning task, wayfinding task in real environment, spatial memory map drawing task. NP tests of	Older adults had problems estimating wayfinding ability; Older adults had significantly more wayfinding errors and stops, no significant differences in spatial memory map drawing task

Note. HA = healthy adults; MTL = medial temporal lobe; NP = neuropsychological tests; RPM = Raven Progressive Matrices; VR = Virtual Reality; WAIS-R = Wechsler Adult Intelligence Scale-Revised

Education and Spatial Memory Performance

Neuropsychological measures of cognitive dysfunction have demonstrated differences due to educational status of the patients (see table 2.9). Significant differences in measures of cognitive functioning between less educated and well-educated adults were found in two studies (Gordon et al., 2008; Springer, McIntosh, Winocur, & Grady, 2005). Preservation of white matter in the frontal lobe was found to be associated with educational level (Gordon et al., 2008; Springer et al., 2005). The majority of studies identified in the literature review controlled for education; however, it is unknown if this is a factor in large-scale spatial memory tasks because studies that examined this variable could not be found. Researchers (Carelli et al., 2011) examined spatial abilities using virtual reality mazes and did not find a significant influence of education on the measures. It is possible that including education as a covariate may lead to a type II error if there is not an association between education and allocentric spatial memory, thus, this must be a consideration in the research design.

Table 2.9 Studies on Education and Spatial Memory Performance

Study	Design	Sample	Measures	Results
Carelli et al., 2011	Comparative	8 patients (63% men, mean age 60.6 years) with focal brain lesions, 40 HA (38% men, mean age 53.7 years)	VR-Maze test, paper and pencil version of VR-Maze test, NP tests including spatial ability (Rey's complex figure copy, Benton's line orientation test, Elithorn's Perceptual Maze test)	Education did not have a significant effect on VR task performance
Gordon et al., 2008	Comparative	60 HA 20 young (20-28 years), 40 elderly (65-81)	WAIS-R box completion, RPM	Higher education was associated with preserved inferior frontal white matter
Springer et al., 2005	Comparative, correlational	14 young (7 men, 7 women, mean age 23.4,) and 14 elderly (9 men, 10 women, mean age 73.9)	MRI during memory tasks	Medial temporal activity correlated with more education in young and with less education in elderly participants

Note. MRI = magnetic resonance imaging; RPM = Raven Progressive Matrices; WAIS-R = Wechsler Adult Intelligence Scale-Revised

Environmental Features of Spatial Memory and Learning

The interaction of HF severity (measured by the Duke Activity Status Index; DASI), covariate factors (age, gender, and education) and environmental features (measured by the Florida Cognitive Activity Scale; FCAS) in HF patients (compared with healthy adults) likely influences the degree of allocentric spatial memory dysfunction. No study in which the relationship between HF severity, environmental features, and spatial memory was examined could be found. It is unclear if spatial memory performance in HF patients is moderated or mediated by biological and environmental factors or if impaired spatial memory influences environmental activities. These components (biological and environmental factors) of the model must be examined systematically, including: animal models of the relationship between diminished cerebral blood flow and spatial memory performance; aspects of protection of spatial memory due to specific environmental features; studies in healthy humans that examine the relationship between spatial memory performance and activity in the hippocampal complex; the relationship between spatial memory performance and damage to the hippocampus in humans; the relationship between brain imaging and presence of HF; and finally the relationship between HF and visuospatial and navigational abilities. The last component (relationship between HF and visuospatial and navigational abilities) was the focus of this study.

Possible Mechanisms for Spatial Memory Preservation

The relationship between the environment and spatial memory performance has been examined in a number of animal studies, often using a rat model. Researchers (Briones et al., 2004; Briones et al., 2000; Sun et al., 2010) completed a set of studies (see table 2.10) and used

different living conditions to house rats following surgery to decrease oxygenation to the brain as compared with rats undergoing sham surgery (no change in cerebral blood flow). In two studies (Briones et al., 2000; Sun et al., 2010), researchers used two different environments: an enriched environment with cognitive and physical aspects (objects to explore or play with, routinely changed to maintain novelty) and a standard environment where rats were housed in standard cages with free access to food and water. Three environments were used in another study (Briones et al., 2004); an enriched environment, a standard environment, and an exercise controlled (standard care and five minutes of forced exercise per day) environment. After being randomized to the different environments, the rats were examined for changes in spatial memory using the Morris water maze (Briones et al., 2000; Sun et al., 2010) and/or examined microscopically for changes in the hippocampal regions (Briones et al., 2004). Ischemic rats housed in standard living conditions were found to have significantly worse swim latency (time to locate goal) and heading error compared with the other groups (Briones et al., 2000; Sun et al., 2010). Neuron density in the anterior CA1 region was significantly decreased; reflecting injury induced degenerative effects in the ischemic rats compared with the sham-surgery rats (Briones et al., 2004). The rats housed in the enriched environment had a significantly greater ratio of synapses to medial CA1 neurons compared with exercise and social control groups, demonstrating a positive treatment effect (Briones et al., 2004). In another study, spatial memory performance was restored in rats housed in an enriched environment (Sun et al., 2010).

Table 2.10 Studies that Examined Environment to Explain Spatial Memory Performance

Study	Design	Sample	Measures	Results
Briones et al., 2004	Experimental design; IV-environment	42 male Wistar rats randomized to SC, EX, and EE groups (8 ischemic, 6 sham in each group)	Microscopic exam	Significantly decreased neuron density of the anterior and medial CA1 area found in the ischemic rats compared with the sham-operated rats indicating more degenerative changes
Briones et al., 2000	Experimental design; IV-environment	38 female Wistar rats randomized to enriched (ischemic 9, sham 10) and standard (ischemic 9, sham 10) environment	Morris water maze, microscopic exam	Dendritic length, segment number and density increased in enriched condition ($p < .05$). Rats in the enriched condition had significantly shorter swim latencies and fewer directional heading errors than rats in standard condition ($p < .05$)

Study	Design	Sample	Measures	Results
Cechetti et al., 2012	Experimental design; 2-vessel occlusion and sham surgery	66 male Wistar rats randomized to experimental (n = 37) and control (n = 29) groups	Morris water maze, histology	Experimental group significantly worse spatial memory than control at 3 and 6 months of testing. CA1 neurodegeneration significantly worse in experimental compared with control rats at 7 days and 3 months
Sun et al., 2010	Experimental design; IV – environment; 2-vessel occlusion and sham surgery	Male Wistar rats randomized into 4 equal groups: sham, sham + EE, model, model + EE	Morris water maze, histology	Chronic cerebral hypoperfusion impaired spatial memory and EE reversed impaired spatial memory
Zhu et al., 2011	Experimental design; 2-vessel occlusion and sham surgery	64 male Wistar rats randomized into 4 equal groups: sham, sham + EE, model, model + EE	Morris water maze; histology	EE reversed LTP impairment

Note. CA1 = Cornu Ammonis 1; CA3 = Cornu Ammonis 3; EE = enriched environment; EC = complex environment; LTP = long-term potentiation; IV = Independent variable; SC = social condition

These studies are important because they demonstrate possible means for protecting spatial memory. Some HF patients are involved in cognitively challenging activities that, due to potentiation of neurogenesis in the hippocampus, may prolong or prevent the development of spatial memory dysfunction. Neurogenesis is a process in which new neurons are formed, and it mainly takes place in the ventricles of the brain and the hippocampus (Gage, 2003). Gage suggests that influences in the environment in the form of increased cognitive, social, and physical activity might improve the connections between neurons within the brain and hippocampus producing neurogenesis. Environmental influences on neurogenesis is an important concept because it may be a factor in the relationship between hippocampal damage in HF patients and the development of spatial memory dysfunction and may lead to a means for improving functional abilities.

Gaps and Limitations in the Literature

Gaps in Knowledge About the Relationship Between Spatial Memory and Learning in HF

During the review of the literature, spatial memory was found to be the least studied domain of cognitive dysfunction in HF patients. Spatial memory and learning are essential elements of an adult's daily functional abilities. However, only two studies were found in the HF literature about spatial memory and its influence on an adult's functional abilities, specifically, getting lost when going to familiar locations. Due to this paucity of knowledge about the proposed relationship between spatial memory and learning and HF patients, research to develop a better understanding of spatial ability in HF and what interventions are needed to improve quality of life, needs to be conducted. A further gap exists in the knowledge of the best

means of measuring spatial memory and learning ability. Research is beginning to demonstrate that virtual reality is an effective measure; however, it is unclear whether virtual reality is measuring allocentric or egocentric spatial ability, or a combination. Research including animal models of chronic cerebral hypoperfusion, spatial memory and learning in healthy adults, and in adults with conditions such as HF that have been shown to be associated with hippocampal damage, needs to be conducted.

Summary: Spatial Memory and Learning in HF Patients

No study was found that specifically examined the relationship between chronic cerebral hypoperfusion in HF patients and allocentric spatial memory. A literature review of research on spatial memory and learning was completed beginning with animal model research in which researchers demonstrated poor spatial memory and learning in rats following decreased blood flow to the brain. The review continued with a descriptive study of ten adults who had major surgery in the medial temporal lobe to include the removal of all or most of the hippocampus. These adults had resultant difficulties with new learning and specifically with ability to navigate. Researchers continued to examine brain lesioned adults, healthy adults, and HF patients using imaging techniques. The researchers found worse spatial memory and learning in those with hippocampal damage compared with adults without hippocampal damage. Next, the literature on visuospatial memory was examined in HF patients with mixed results of differences between healthy adults and HF patients. Further these studies examined egocentric visuospatial rather than allocentric spatial ability. Other than two qualitative articles that identified getting lost as a problem in patients, little could be found on allocentric spatial ability in HF. Variables including age, gender, and education, that may help to explain spatial

ability were examined. A number of studies demonstrated a relationship between age and spatial ability; however, findings about associations with gender and education were mixed. The relationship between poor spatial memory and learning and decreased cerebral blood flow was further examined in animal models. Introducing the rats to an enriched environment led to improved spatial memory and learning.

Most researchers who studied spatial memory and learning in HF patients, focused their research on brain pathology or visuospatial abilities. Neuroimaging and neuropsychological tests were the methods most often used to examine brain pathology and visuospatial ability in HF patients. Results included lower cerebral blood flow and worse medial temporal lobe damage in HF patients compared with healthy adults. Further, in the majority of the studies in which researchers examined visuospatial ability, HF patients had worse visuospatial ability than healthy adults. Pressler, Subramanian, and colleagues (2010) did not find worse visuospatial ability; however, poor visuospatial ability was an independent predictor of mortality in HF patients. Researchers examined the relationship between HF; the covariates age, gender, and education; and spatial memory and learning with mixed results. In most of the studies examined, men and younger adults had better spatial memory performance; education was not often examined in the allocentric spatial performance literature, and when it was, no significant difference with respect to level of education, other than differences in medial temporal lobe activity, was found. This review covers sixty articles that examined different aspects of explanatory variables for allocentric spatial memory and learning that were used to develop a theoretical framework for examining spatial performance in HF patients and the optimal method to identify spatial memory and learning dysfunction. While this review provided a

theoretical basis for a relationship between spatial memory performance and HF, consensus in the articles about the explanatory factors or optimal measurement of spatial memory and learning was not found. Many studies were limited by screening measures, number of study participants, the young age of the healthy adults, a higher predominance of men enrolled in studies, samples from one particular location (school or hospital) lack of studies conducted over time, and finally, most did not differentiate the type of memory dysfunction that was affected or how dysfunction influenced spatial learning. Future studies are needed to examine spatial ability in patients with HF to determine the best explanatory factors, determine the best possible methods for assessment of spatial performance, and ultimately to design interventions to improve patients' functional abilities.

CHAPTER III

Methodology

The purpose of Chapter III is to describe the methods used to conduct this study. The chapter is organized into five main sections including: research design, study sample, procedures to examine spatial learning and memory in HF patients, measures to examine study aims and hypotheses, and statistical analyses of data. The procedure for the enrollment of participants and the components of the design that enabled the hypotheses to be tested are described in detail, including criteria for enrollment, recruitment, testing procedures, differences in spatial memory performance as measured by large-scale and small-scale measures, and the variables that explain spatial memory performance. A description of the measures used in the study and methods for statistical analyses are also presented.

Research Design

The research design for Aim 1 was a comparative design, and repeated measures analysis of variance (ANOVA) was used to examine the ability of an individual to learn and remember the location of a hidden platform as a function of allocentric spatial memory performance. Aim 2 used a descriptive design to examine the relationship between allocentric spatial memory (large-scale testing) and egocentric spatial memory (small-scale testing). Aim 3 used a descriptive design to examine the factors that describe allocentric spatial memory performance in a sample of older (≥ 55) HF patients and healthy adults.

Study Sample: Size and Criteria

A total of 64 participants were enrolled in the study after obtaining Institutional Review Board (IRB) approval, including 32 men and women with HF recruited from a Midwestern HF clinic and 32 healthy men and women who were matched in age to the HF patients. The healthy adults were recruited through family members or friends of the patients, through advertisements placed in clinics, and through a website of a large tertiary care Midwestern university. The sample size was based on a power analysis for the largest sample size needed for the hypotheses (hypothesis 1 for all participants). The effect size was estimated to be large from a study conducted by the authors of C-G Arena (Skelton, Bukach, Laurance, Thomas, & Jacobs, 2000). The power analysis for aim 1, hypothesis 1, was completed using 80% power, an alpha of .05, and a large effect size for independent-samples t-test indicating a sample size of 26 participants per group was needed (Cohen, 1992). The power analysis for aim 1, hypothesis 2, was completed using 80% power, an alpha of .05, and a large effect size for repeated measures ANCOVA indicating a sample size of 26 per group was needed (Cohen, 1992). The power analysis for aim 2, hypothesis 3, was completed using 80% power, an alpha of .05, and a large effect size for partial correlation indicating a sample size of 28 was needed. Aim 3 is an exploratory aim, thus a power analysis was not conducted. (Cohen, 1992).

Patients who were enrolled in the study had a documented diagnosis of chronic (over six months) HF, systolic dysfunction as documented by echocardiogram or other diagnostic procedures in past 2 years, LVEF ≤ 40%, NYHA functional class II or III, and Stage C HF. These criteria ensured that study patients had HF with decreased cardiac output over time, and that their risk for chronic cerebral hypoperfusion was significantly greater than that of healthy

adults. Patients were optimized on medical therapies as determined by the physician. Healthy adults had no history of major medical disease (e.g. uncontrolled hypertension, diabetes mellitus, active cancer, chronic obstructive pulmonary disease, and angina) and were matched in age to the HF patients. Healthy adults with controlled cardiovascular risk factors (e.g., hypertension, hyperlipidemia) were eligible to be enrolled in the study.

Inclusion Criteria

In addition to the inclusion criteria described in the previous paragraph, inclusion criteria included: 1) being 55 years of age or older; 2) being able to read the English language; 3) being able to hear normal conversation; 4) having intact vision (20/40 or better with correction); and 5) having access to a working telephone in order to schedule visits.

Exclusion Criteria

Exclusion criteria were generated with the intention of limiting confounding factors, particularly those that might change the relationship between the independent variables and spatial memory, and ensuring that participants had the ability to complete computer testing. Conditions that may lead to confounding effects are those that change perfusion to the brain, affect cognitive functioning, or limit the ability to move the joystick or see the computer screen (Davis et al., 2008; Woo et al., 2003). Exclusion criteria included: 1) a history of myocardial infarction or new-onset cardiomyopathy within the past 6 months; 2) a documented history of or current drug abuse, 3) alcohol abuse with alcoholic encephalopathy; 4) a major psychiatric diagnosis that was present before the HF diagnosis; 5) having been diagnosed with a central nervous system disorder (e.g. Alzheimer's, other dementia, stroke, epilepsy, history of head injury with loss of consciousness longer than 30 minutes, Parkinson's disease, or other central

nervous system movement disorders); 6) hepatic encephalopathy; 7) a chronic kidney disease requiring hemodialysis or peritoneal dialysis; 8) a congenital heart disorder; 9) a disabling physical condition that impairs the ability to move the joystick (e.g. rheumatoid arthritis); 10) terminal cancer; 11) prisoner status; and 12) a score of less than 24 on the Mini-Mental State Examination (MMSE; Folstein, Folstein, & McHugh, 1975; Lezak et al., 2004).

Participant Recruitment and Enrollment

The principal investigator (PI) worked with Dr. Koelling, MD, Director of the HF Program at the University of Michigan that provides care to 3500 HF patients per year. Patients were recruited from two sources; first, from a previous study on which the PI worked (participants expressed an interest in volunteering for future research projects during home visits), and second, from a list of eligible patients identified in the HF clinic by Dr. Koelling or his designee. Names of eligible patients were provided to the PI who then contacted all potential patients from both sources via telephone and invited them to participate in the study. Potential healthy adults were identified during initial contact with enrolled patients by asking if they had a family member or friend who might be interested in enrolling in the study. Contact information was provided to the enrolled patient for potential healthy adults to call if interested in order to avoid making them feel pressured to enroll. Advertisements in the form of flyers for healthy adults were placed per policy after IRB approval in UMHS and on UM campus that included PI contact information. Participant recruitment was discussed with the advisor every other week in order to maintain steady targeted enrollment of similar adults (age, race, and ethnicity).

The PI received training on neuropsychological test administration, scoring, and interpretation for all measures used in this study from a designee of Dr. Giordani, a

neuropsychologist and professor of psychology prior to beginning data collection. Mock recruitment, enrollment, and data collection was completed with a co-investigator and PhD nursing students prior to beginning enrollment

Procedures to Examine Spatial Learning and Memory in HF Patients

During initial contact (see appendix A for detailed procedure), inclusion and exclusion criteria were verified, overall objective and specific aims of the research study were verbalized, including expected benefits and potential risks, and appointments were scheduled in participants' location of choice. Necessity of having an uninterrupted session with the participant was emphasized, and ability to accommodate a quiet setting was ascertained. In situations in which the participant could not guarantee an uninterrupted session, it was determined if a research assistant (a graduate nursing student recruited to assist with potential interruptions) could manage interruptions; if not, the participant was thanked for their time and interest and informed that they could not participate in the study because it was imperative to have an uninterrupted testing session for results to be valid.

Procedure for First Visit

During the first home or agreed upon location appointment, the informed consent statement was reviewed, questions were answered, and signatures were obtained (25 minutes). The potential participant was then screened using the Mini-Mental State Examination (MMSE; 5 minutes), and participants with a score of less than 24 (O'Connor et al., 1989), an indication of possible dementia, were excluded from the study. Potential participants were also screened with a Snellen eye chart (5 minutes) and needed to achieve at least 20/40 vision with corrective lenses to be enrolled in the study.

Computer-Generated Arena Procedure.

Participants were given a five minute break after completing the informed consent and screening measures before starting the computer testing session. The C-G Arena is a virtual reality computer software program that has three rooms in which the participants maneuver using a joystick. Detailed instructions were given to the participants on how to move the joystick in order to navigate within the virtual rooms and on what needed to be accomplished in each of the three virtual rooms.

Computer training and testing occurred in three different rooms (practice, training, examination rooms) using the C-G Arena software which was installed on a study delegated, laptop computer equipped with a joystick. In addition to the three rooms, participants would be transported, by touching the space bar, to a waiting room between the training trials and examination trials. The objective of the practice room was to practice moving the joystick; participants were informed that there were no targets in the practice room. The objective of the training room was to navigate to a visible target in less than 30 seconds at least once during two 30-second sessions. The objective of the examination room was to find the invisible target and once the location was determined, participants were instructed to find the invisible target as quickly as possible via the most direct route.

The first room was a simulated practice room in which the PI demonstrated how to use the joystick and then asked participants to practice navigating using the joystick. Participants had three minutes to become familiar with how to move the joystick in this room and were offered further sessions, if needed, to ensure that participants felt comfortable using the joystick prior to entering the training room. The practice room had four different solid colored

walls; red, yellow, blue, and green, a dark grey floor, and a light grey ceiling. There was a red-brick, circular half-wall within the outer four walls of the room; no cues where on the walls in this room.

When confident with how to move the joystick or at the end of three minutes, participants were instructed to press the space bar to enter the second room, the training room. The training room had four blue, solid colored blue walls with a light grey ceiling and dark grey floor and the red-brick, circular half-wall. There was a bright blue target visible in the center of the room on the dark gray floor. Participants were instructed to navigate to the visible target using the joystick. After participants successfully navigated to the visible target, they were transported back to the waiting room by pressing the space bar. Participants were then offered another practice session of three minutes in the waiting room before moving on to the examination room. No participants choose to repeat the practice session.

When ready to move to the examination room, participants were instructed to press the space bar. Pressing the space bar transported participants into the examination room to begin six timed trials. The examination room had four solid blue walls with different pictures on each of the walls. The ceiling and floor were gray as in the training room. The same red-brick, circular half-wall, which appeared to be waist high from the view of the participants, was within the four walls of the examination room. Pictures on the walls included on the first wall a large centered desert scene that covered about half of the wall. The next wall to the right had two pictures, the first was a close-up of flowers with a bee flying nearby, and the second was a swimmer in a pool under water. Continuing to the right, the next wall had one picture centered on the wall of numerous bald heads with one face looking up at the camera. The last wall had

two pictures, the first of a number of horses in a field and the second of a small dog running through snow. The invisible target was between the flowers and the small dog (parallel walls), just to the left of the desert scene picture (connecting wall).

During the examination trials, the participants were transported to different, random start locations within the circular half-wall. Participants were instructed that the invisible target would be in the same location each time the examination room was entered, and that once the location was found by "walking" on it, the target would become visible. Each time the participants found the target, a dinging noise was heard, and the participants were not able to leave the space that the target occupied. Participants were encouraged to make sure that they remembered the location of the invisible target by looking around the room once while "standing" on the target. The participants were then instructed to press the space bar when they felt confident that they knew the location of the target to transport back to the waiting room. If the target was not located within three minutes, participants were automatically transported back to the waiting room. This procedure was repeated another five times for a total of six 3-minute trials with 1-minute waiting room time, between trials, for a total of 24 minutes for the test.

Study Questionnaires

The participants were given a five minute break following computer testing after which study questionnaires were completed. The study forms including demographics, the DASI, and the FCAS were collected using an alternating schedule to control for the effects of testing order (see schedule in appendix A). Following the completion of study forms (approximately 20

minutes), participants were asked to confirm their appointment times for the following day and thanked for their time and participation.

Procedure for Second Visit

During the second day visit, participants again completed a learning phase of six trials using the same procedure as the first day with the exception of the visible target trial, which was not completed (total of 24 minutes). On the second day, the participants also completed a probe trial to measure spatial memory. The probe trial involves removing the invisible target and measuring the amount of time the participants spend in the quadrant in which the target should have been located. After a five minute break, the neuropsychological tests were conducted using one of four alternating schedules (see appendix A for timing of measures and break) including:

1. Consortium to Establish a Registry of Alzheimer's Disease (CERAD) figure copy test and figure memory recall (15 minutes)
2. Hopkins Verbal Learning Test-Revised (HVLT-R) with delayed recall (20 minutes)
3. Corsi Block-tapping test (15 minutes)
4. Wechsler Adult Intelligence Scale-Revised (WAIS-R) Digit Span (15 minutes)
5. Trail Making Test Parts A and B (TMT-A, TMT-B) (10 minutes)
6. Controlled Oral Word Association (COWA) (10 minutes)

After completion of the neuropsychological tests participants were given a gift card as an incentive and thanked for his/her participation in the study.

All testing was completed in a quiet room (phone and television turned off if present) in participants' home or mutually agreed upon location with no distractions during testing.

Household members were also informed of the importance of not interrupting the sessions. Large-scale testing using the C-G Arena was completed on a laptop computer (supplied by the principal investigator) with a joystick to enable easy movement within the virtual reality environment. Neuropsychological tests were completed following the administration of the C-G arena, and all questions were read to participants by the investigator in order to standardize the administration procedures and ensure complete data collection.

The data collection took no longer than 90 minutes for each visit. Rest periods were offered before and after C-G Arena testing on both days, after 40 minutes of neuropsychological testing on the second day, and if participants showed any signs of fatigue during the visits. If a participant had felt fatigued despite rest periods, an option to discontinue data collection would have been offered (this did not occur). No participants withdrew from the study after signing the informed consent statement. Background information (the Charlson Co-morbidity Index) was obtained from patients' medical records in the clinic setting after the informed consent statement was signed. Following data collection from the study participants, measures were scored, entered into the data base, verified, and screened for errors.

Measures to Examine Study Aims and Hypotheses

Computer Testing of Spatial Memory Performance

At present, there is evidence that supports that spatial memory dysfunction may be a concern in HF patients. Research about how best to measure allocentric spatial memory is in the early stages. However, virtual reality programs are increasingly being used to measure spatial memory because they are able to use an allocentric frame of reference for navigation and have been shown to be reliable when compared to real life testing (Cushman, Stein, &

Duffy, 2008). Brain activity can be examined during virtual reality testing to determine which specific areas of the brain are active during certain types of activities, such as what structures are most active when performing an allocentric spatial memory task. Therefore, virtual reality testing may serve as the most effective tool for assessing any differences in brain function between healthy adults and HF patients and for identifying whether or not spatial memory dysfunction is significantly linked to HF.

Large-scale Spatial Memory Measures

Large-scale spatial memory and learning was determined using the Computer-generated (C-G) Arena computer program, a unique computerized virtual reality program developed by the University of Arizona Anxiety Research Group (Jacobs et al., 1997). Virtual reality computer programs have been used as large-scale measures of allocentric spatial memory performance.

Computer-Generated Arena. Davis and colleagues examined differences in navigation using the C-G Arena, a virtual reality program that measures place learning, a type of spatial memory performance (Davis et al., 2008). This virtual reality program was chosen for this study because of its ability to measure spatial navigation using a large scale allocentric frame of reference.

Two studies (Laurance et al., 2002; Skelton et al., 2000) supported internal validity of the C-G Arena. Laurance and colleagues (2002) found positive Pearson correlations of .58 to .76 between C-G Arena and a real-world analog of the Morris Water Maze, suggestive of the accurate use of the C-G Arena to measure of spatial ability in the actual world. Skelton and colleagues determined construct validity of the C-G Arena by correlating an average z-score of the distance on invisible target and probes trials with the distance on invisible trials ($r = -0.91$)

and with the distance on visible target trials (r = 0.08), both of which were expected results. Further, Pearson correlation was conducted for path length for invisible target and spatial memory questionnaire items (r = .49 to .5), room reconstruction (r = -.73), and probe trial (r = -.64). Notably, low Pearson correlations were found between invisible target measures and visible target measures (r = .01 to -.14). The measures that were analyzed were time to target, measured in seconds to find the hidden platform from when the participants entered the room until the target was reached; path length, the unit distance from where the participants started the trial until the target was reached; and heading error, the angle formed when two vector lines are drawn from the start position with the first vector line as the initial heading the participant took from start and the second as the direct path from the vertex to the target. Heading error was the angle resulting from two lines heading out from the vertex; line one was the direct path to the target and line two was the initial path. Thomas and colleagues (2001) examined neural activity intensity in the hippocampus using fMRI during the C-G Arena task in two participants, one who did and another who did not learn the location of the platform. Hippocampal neural activity intensity during fMRI was significantly greater in the learned placement vs. the unlearned placement conditions.

Validity and reliability of virtual reality programs. Matheis and colleagues (2007) examined the ability to measure memory using a virtual reality environment compared with standard memory testing. Forty adults were enrolled, 20 with traumatic brain injury and 20 healthy adults matched on age, gender, and education. A virtual reality computer program named VR Office was used to assess the memory of the study participants and compared with

standard neuropsychological tests. Construct validity was supported by a significant relationship between VR Office and a standard measure of memory ($r = .7$, $p < .001$).

Another recent study (Parsons & Rizzo, 2008) examined the relationship between standard neuropsychological tests and a virtual city environment in 30 healthy adults (mean age 24.97, 15 men, & 15 women). Analyses supported construct validity of the Virtual Reality Cognitive Performance Assessment Test (VRCPAT) among healthy adults; tests of learning and memory correlated with the VRCPAT at $r = .65$ to $.73$ ($p < .01$).

Cushman and colleagues (2008) demonstrated construct validity with a strong correlation ($r = .73$) between a virtual reality navigation task and real world navigation. Construct validity was further supported by significant differences between real world navigation scores and virtual reality scores among the four groups with the best scores in the young adults [$F(1,76) = 19.65$, $p < .001$; Cushman et al., 2008]. It should be noted that Cushman and Colleagues did not use C-G Arena during testing and validity and reliability may be different than what was found in their study.

Neuropsychological Testing

The battery of neuropsychological tests used in this study included: a measure of global screening (MMSE); two measures of attention (WAIS-IV Digit Span, TMT-A); two measures of executive function (TMT-B, COWA); a measure of short-term memory (HVLT-R); and three measures of visuospatial memory (Corsi Block-tapping, CERAD figure copy, figure memory recall). These small-scale measures are fully explained below. Multiple studies have shown an increased occurrence of cognitive dysfunction in HF (Callegari et al., 2002; Elkadi et al., 2005; Hoth et al., 2008; Pressler, Subramanian et al., 2010; Sauve et al., 2009; Trojano et al., 2003;

Vogels, Oosterman, van Harten, Sheltens et al., 2007; Wolfe et al., 2006). Most of these studies used methods to examine visuospatial abilities using egocentric rather than allocentric tasks. The Corsi Block-tapping and CERAD figure copy and figure memory recall are two neuropsychological tests that have been used as small-scale egocentric spatial memory measures. One of the aims of this study was to determine if allocentric and egocentric measures of spatial ability correlate. All instruments that were chosen for this study have documented validity and reliability (see individual measures).

Mini-Mental State Examination. The MMSE is a measure used to examine changes in mental status, and to assess global cognition (Lezak et al., 2004). Reliability of the MMSE was r = .89 for test-retest (24 hour) with the same examiner and r = .83 for inter-rater reliability. Concurrent validity of the MMSE, Pearson r was .78 (verbal IQ) and .66 (performance IQ) when compared with the Wechsler Adult Intelligence Scale (WAIS; Folstein et al., 1975). The measure was analyzed using a summary score, with a possible range of 0 – 30, with 30 being better global cognitive function.

Corsi Block-Tapping Test. The Corsi Block-tapping was designed to measure short-term visuospatial memory (Mauro et al., 2007; Piccardi et al., 2008). Nine wooden blocks (3 cm by 3 cm) are numbered on one side, with numbers facing the experimenter (Piccardi et al., 2008). The blocks are placed on a board, measuring 25 cm by 30 cm in a random order. The experimenter touches each block for 1 second in a specific order, starting with two blocks. Participants must touch the blocks in the same order as demonstrated. This procedure is repeated, increasing by one block with each repetition, until a participant misses four out of five trials of the same sequence of blocks. The procedure is repeated, except the blocks must be

tapped in the reverse order from that which the experimenter demonstrated. A score is then entered that corresponds to the largest sequence of blocks correctly demonstrated forward and backward (Piccardi et al., 2008). Adults with Alzheimer disease had lower Corsi Block-tapping scores when compared with healthy adults during addition of sequence lengths (Lezak et al., 2004). Participants' ability to accurately tap blocks was significantly influenced by sequence length ($F\ 6, 54 = 42.4$, $p < .0001$) (Fischer, 2001). An age effect was found (Beigneux, Plaie, & Isingrini, 2007) for the Corsi Block-tapping test [$F(2,75) = 13.44$, $p < .001$)]. Significant [$F(2,75) = 36.61$, $p < .0001$] effects were found when education and vocabulary score were entered as covariates into analysis of covariance (ANCOVA). Mauro and colleagues (2007) found a significant albeit small association between education and the Corsi Block-tapping test ($r = .12$, $p = .020$). The measure was analyzed using a total score with a possible range of 0 – 16 for forward block-tapping and 0 – 16 for backward block-tapping scores; higher scores indicated better performance (Lezak et al, 2004). Many studies were found that used the Corsi Block-tapping test; however none were found that reported reliability and validity data.

Wechsler Adult Intelligence Scale-IV: Digit Span. Digit Span was designed to measure attentional capacity and requires short-term retention (Lezak, 2004). Digit Span is not sensitive to early dementia, but is affected in later stages of dementia and in those with frontal lobe involvement (Lezak, 2004). Digit Span involves repeating a sequence of numbers verbalized by the examiner, exactly as stated (Digit Span forward), in the reverse order (Digit Span backward), and in ascending order (Digit Span sequencing). The examiner begins with a sequence of three numbers (two numbers for sequential span) and adds another number to the sequence after each correct response for up to nine numbers (Lezak, 2004). Only being able to complete a

sequence of three is considered impaired, four is borderline, five is marginal normal, and six or more is within normal limits; age has minimal influence on scores (Lezak, 2004). The measure was analyzed using a total score with a possible range of 0 – 48 with higher scores indicating better performance. A study by Pressler, Subramanian, and colleagues (2010) found no significant differences between HF patients, medical control participants, and healthy adults (forward – $F = .1$, $p = .930$; backward – $F = 2.2$, $p = .120$; scaled – $F = .4$, $p = .700$).

Trail Making Test Part A. The TMT-A was designed to measure visual scanning and tracking and attention (Lezak et al., 2004). Patients are given a sheet of paper with circled numbers from 1 to 25, randomly positioned on the paper. The objective is to connect the numbers beginning with one and ending at 25 as quickly as possible. Average score for part A is 29 seconds (Reitan, 1955). The test is considered positive for cognitive deficits in patients who take longer than 78 seconds for part A (Alsworth, n. d.). Construct validity was shown through correlation with caudate atrophy in Alzheimer Disease of $r = .72$ for part A (Lezak et al., 2004). Reliability coefficients were generally greater than $r = .60$, (many $r > .80$ and some $r > .90$) for both parts of the TMT (Lezak et al., 2004). Scores on TMT-A differentiated brain damaged adults with non-brain damaged adults ($t = 4.68$; $p < .001$) (Reitan, 1955). The measure was analyzed using a total score of time in seconds, with higher scores indicating worse performance. Part A takes approximately three minutes to explain and administer in a cognitively intact adult.

Trail Making Test Part B. The TMT-B was designed to measure visual tracking and cognitive flexibility (Lezak et al., 2004). Part B adds circled letters to the numbers, and the patient needs to alternate between letters and numbers, e.g. 1-A-2-B-3-C, etc. Average score for part B is 75 seconds. The test is considered positive for cognitive deficits in patients who

take longer than 273 seconds for part B (Lezak et al., 2004). Construct validity was shown through correlation with caudate atrophy in Alzheimer Disease of r = .80 for part B (Lezak et al., 2004). Reliability was demonstrated to be greater than r = .60 in almost all studies (many found r > .80, some found r > .90) for both parts of the TMT (Lezak et al., 2004). Reitan (1955) found significant differences in brain damaged and non-brain damaged adults using TMT-B ($t = 5.33$; $p < .001$). The measure was analyzed using a total score of time in seconds, with higher scores indicating worse performance.

Controlled Oral Word Association. Controlled Oral Word Association was designed to measure executive function. Adults with frontal lesions, especially on the left and those with stroke in the left hemisphere generally have lower scores than healthy adults (Lezak et al., 2004). Reliability was determined using internal consistency (Coefficient alpha = .83) and test-retest (r = .74) (Ruff, Light, & Parker, 1996). Education had a significant influence ($F_{2,336} = 16.21$, $p < .001$) on COWA scores and explained 8% of the total variance (Ruff et al., 1996). The COWA is administered using a specific group of three letters, one at a time, for which the participant must think of as many words as possible starting with the specific letter over the course of 60 seconds (Lezak et al., 2004). Groups of letters were standard on the different forms and were alternated throughout the study in sequential order such that the first participant received form A (letters C, F, L); the second participant received form B (letters P, R, W); the third participant received form C (letters F, A, S); and then the sequence would repeat. Prior to being given the letter, the participants were told they could say any word except proper nouns or the same word with different endings (e.g. eat and eating). The measure was analyzed using a total score of all words identified for the three letters, plus a correction factor

for age and education with a possible range of 0 – 12 (Lezak et al., 2004). Higher scores indicated better performance.

Hopkins Verbal Learning Test-Revised. The HVLT-R was designed to measure short-term and long-term memory. An advantage of HVLT-R is there are six forms that are comparable for learning and recall, and the test is well tolerated in elderly patients and in those with dementia (Benedict, Schretlen, Groninger & Brandt, 1998). Each of the forms was made up of a list of 12 words (three categories of four words) that were read to the participant who was asked to repeat the words back to the examiner. The procedure was repeated two more times with each trial scored individually (possible score of 12) and totaled (possible score of 36). After a 20 minute delay the participant was asked to recall the list and then recognize the words in a list of the 12 target words plus 12 newly added words (Lezak et al., 2004). The measure was analyzed using the total score with a possible range of 0 – 36, and the delayed recall score with a possible range of 0 – 12. Higher scores indicated better performance. Sensitivity and specificity were high for patients with AD and healthy adults (84% and 94%, respectively) (Shapiro, Benedict, Schretlen & Brandt, 1999).

CERAD Constructional Praxis Design Copy. Two subtests that measure constructional praxis (figure copy and figure memory recall) in the CERAD were designed to assess visuospatial and constructional abilities (Fillenbaum, Heyman, Huber, Ganguli, & Unverzagt, 2001). The patient was asked to copy five figures increasing in complexity and to draw the same figures from memory after a 20-minute delay (sometimes referred to as figure copy test and figure memory recall; Pressler, Subramanian et al., 2010). Figure memory recall, when combined with word list recall in a linear regression model, distinguished depression and Alzheimer's with a

receiver operating characteristic of .91; Alzheimer's patients showed poorer recall (Kunig et al., 2006). The measure was analyzed using the total score with a possible range of 0 – 11 for figure copy and 0 – 14 for figure memory recall. Higher scores indicated better performance.

Ackl and colleagues (2005) determined patients with Alzheimer's disease had significantly poorer constructional praxis scores (figure memory recall) when compared with adults with mild cognitive impairment and with healthy adults ($p < .05$). Significant group differences were found, controlling for age, using ANCOVA [$F(2,51) = 27.9$, $p = .001$] for figure memory recall, but not figure copy. Researchers (Fillenbaum et al., 2001) found inter-rater reliability for CERAD subtests between .76 and 1 with most correlation coefficients above .90. Significant differences were not found in figure copy scores between men and women.

Environmental Factors - Cognitive and Social Activities

The FCAS is a 25-item measure on a 6-point response scale that was used to determine environmental factors. Schinka and colleagues (2005) developed the FCAS as a measure of self-reported cognitive activities and as a means to support the potential protective influence of cognitive activities on cognition. The FCAS was examined in two separate studies (Schinka et al., 2005; Dotson, Schinka, Brown, Mortimer, & Borenstein, 2008), first on a group of white older adults (60-84 years) and then on a group of age-matched African-American older adults. Both of these cohorts were living independently during the time of the study. Cognitive activities were determined by the researchers (Dotson et al., 2008; Schinka et al., 2005) to have a protective effect on cognitive decline after controlling for age, gender and educational level. Internal consistency (reliability) showed a Cronbach's alpha of .65 in the initial study (Schinka et al., 2005) and a Cronbach's alpha of .68, .53, and .55 for the cognitive activity scale, higher

cognitive scale, and frequent activities scale, respectively in the second study (Dotson et al., 2008). The FCAS looks at many different activities that range from grocery shopping to playing board games and this may explain why the reliabilities are < .70 (Schinka et al., 2005). Pressler and colleagues (2011) found a Cronbach's alpha of .77 in 44 HF patients during baseline testing and .76 at 12-week follow-up testing. The measure used a summary cognitive activity score. Cronbach's alpha coefficient was computed in the current sample for FCAS to estimate internal consistency and reliability of the scales. Reliability was found to be lower in the FCAS (coefficient alpha .65) than the minimum recommended level of .7 suggested by Nunnally (1978). This may be due to the heterogeneous items on the FCAS. The mean inter-item correlation for the FCAS (.36) was between the optimal value range of .2 - .4 (Briggs & Cheek, 1986).

Duke Activity Status Index

The DASI is a 12-item scale that was used to assess perceived functional capacity. Validity evaluation of the DASI was initially conducted on cardiac patients and compared with peak oxygen uptake (Hlatky et al., 1989). Patients were interviewed during the developmental phase of the measure, and Spearman correlation was high ($r = .81$; $p < .0001$). During the validation phase, patients were given a questionnaire to complete instead and construct validity was more moderate ($r = .58$, $P < .0001$). Reliability was determined with Cronbach's alpha in coronary heart disease patients before and after undergoing angioplasty compared with another stable group of coronary heart disease patients ($\alpha = .89$ and .86, respectively; effect size .75, $p < .001$; Alonso et al., 1997). Reliability (Cronbach's alpha 0.82) was determined in 249 HF patients (Pressler, Subramanian et al., 2010). A calculated DASI score was used for

determining perceived functional capacity in the current study. Cronbach's alpha coefficient was computed in the current sample for the DASI to estimate internal consistency and reliability of the scales. Reliability was found to be high in the DASI (coefficient alpha .86), higher than the minimum recommended level of .7 suggested by Nunnally (1978). Mean inter-item correlation of .36 (range -.03 to .83) was found, which was between the optimal value range of .2 - .4 (Briggs & Cheek, 1986).

The Charlson Comorbidity Index

The Charlson Comorbidity Index was developed to predict mortality for patients enrolled in longitudinal studies (Charlson, Pompei, Ales, & MacKenzie, 1987; Quan et al., 2011), and was used as a measure of comorbid conditions in HF patients. The Charlson was found to have satisfactory ability to discriminate outcomes, (C statistic = .73 to .88) specifically in hospital mortality of patients (Quan et al., 2011).

Sociodemographic Variables

Sociodemographic variables were collected using the demographics form to include: age, gender, ethnicity, race, marital status, education, employment status/occupation, living arrangements, handedness, height, weight, smoking/alcohol history, medication usage, and menstrual history.

Statistical Analyses of Data

Descriptive statistics (means, standard deviations, ranges, and frequencies) were computed for all variables. Inter-rater reliability using Cronbach's alpha was estimated for the FCAS and for the DASI. Scale scores were computed according to the authors' specifications on the FCAS, DASI, and the neuropsychological tests. Relationships between sociodemographic

variables and other study variables were evaluated using Pearson's correlation, independent t-test, and Chi-square tests, depending on the level of data. Pearson's correlation coefficients including tolerance and variance inflation factor (VIF) were examined to assess multicollinearity among the independent variables ($r \geq 0.80$ according to Polit, 1996) for aim 3.

Aim 1, Hypothesis 1: Allocentric spatial memory is poorer in HF patients compared with age-matched healthy adults, was tested using independent-samples t-test to examine differences between the two groups for the amount of time spent in the quadrant during probe testing.

Aim 1, Hypothesis 2: Allocentric spatial learning is poorer in HF patients compared with age-matched healthy adults, was tested using repeated measures ANCOVA to examine differences in the six learning trials using path length, time to find target and heading error.

Aim 2, Hypothesis 3: Allocentric and egocentric measures of spatial memory have a non-significant relationship, was tested using Pearson product-moment correlation coefficient and partial correlation to examine the relationship between egocentric and allocentric frames of reference for spatial memory performance.

Aim 3: The influence of gender, group, perceived cognitive activity, and perceived functional capacity on spatial memory performance in older participants with and without HF, was tested using simultaneous multiple regression.

Significance level was set at $p < .05$ for all statistical analyses. The use of multiple measures to evaluate the different domains of memory may increase the likelihood of finding significant results. However, it was decided not to use a more stringent significance level because little is known about spatial memory in HF patients at this time.

Post-hoc analyses were conducted to further examine the significant influence of age on measures of spatial memory and learning using ANCOVA, with gender entered as a covariate in the analyses. Next, spatial memory and learning was tested using t-test of mean scores by gender (men and women) for the full sample of participants.

CHAPTER IV

Results

Chapter IV reports the results of data analyses, conducted to examine spatial learning and memory, after the data were collected as described in Chapter III. The chapter covers the descriptive analyses that compare demographic and study variables between the two groups, the analyses that were performed to meet the study aims and test the hypotheses outlined in Chapter I, and post-hoc analyses that were performed to provide further understanding of the complex components of spatial learning and memory.

Analyses: Description of Demographics and Study Variables

Characteristics of study participants. Demographic variables were analyzed to determine if significant differences existed between the two groups of participants (see Table 4.1). As discussed in Chapter III, Methods, 32 HF patients were enrolled from a HF clinic and 32 healthy adults were enrolled from advertisements and referrals. The HF patient and healthy adult groups were similar in age ($p = .476$). The HF patient group had more men (20 of 32 patients) and the healthy adult group had more women (19 of 32 adults) but the difference in gender was not statistically significant ($p = .080$). The HF patient and healthy adult groups were similar with respect to race and ethnicity ($p = .435$, $p = 1.000$, respectively). Fewer HF patients were married (19) than were healthy adults (25) but this difference was not statistically significant ($p = .106$). Education was significantly different between the two groups with the HF group having a lower mean years of education than the healthy adult group (14.4 years

compared with 17.3 years, respectively; t = -4.69, p < .001). Further, the HF group had fewer college graduates than the healthy adult group (20 of 32 compared with 29 of 32, respectively; X^2 = 7.1; p = .008).

The HF patients were a symptomatic group with a mean LVEF of 25.9 and the majority were classified as NYHA class II (63%). Most HF patients (84%) had at least one medical diagnosis other than HF, as indicated by the Charlson Comorbidity Index with a range of 1 to 6 medical diagnoses. Fifty percent of the HF patients had two or more comorbid conditions (other than HF). A majority (91%) of HF patients had implantable cardioverter defibrillator (ICD) devices and 25% had implanted pacemakers. Many HF patients with ICDs (41%) also were being treated with cardiac resynchronization therapy (CRT) including biventricular pacemakers.

Characteristics of activity: DASI and FCAS. In addition to demographic variables, HF patients and healthy adults were compared with respect to a number of functional variables (See Table 4.1). The HF patients had significantly worse DASI scores compared with the healthy adults (t = -9.90, p < .001). As stated in Chapter III, Methods, while the DASI is a measure of perceived functional status, it has been correlated with peak oxygen uptake; this indicated poor functional ability in this particular group of HF patients. Further, the HF patients were involved in significantly fewer cognitive and social activities than the healthy adults (t = -2.55, p = .014).

Table 4.1 Demographic and Clinical Variables of HF Patients and Healthy Adults (n = 64)

Characteristic	Total (n = 64)	HF Patients (n = 32)	Healthy Adults (n = 32)	Chi-square or t-statistic (p-value)
Age, mean ± SD	67.6 ± 8.7	68.3 ± 8.2	66.8 ± 9.2	.717 (.476)
Range	55-89 years of age	55-89 years of age	55-83 years of age	
Gender, n (%)				3.065 (.080)
Men	33 (51.6)	20 (62.5)	13 (40.6)	
Women	31 (48.4)	12 (37.5)	19 (59.4)	
Race, n (%)				1.664 (.435)
African-American	8 (12.5)	5 (15.6)	3 (9.4)	
White	55 (85.9)	26 (81.3)	29 (90.6)	
American Indian	1 (1.6)	1 (3.1)	0 (0)	
Ethnicity, n (%)				0.000 (1.0)
Hispanic	2 (3.1)	1 (3.1)	1 (3.1)	
Non-Hispanic	62 (96.9)	31 (96.9)	31(96.9)	
Marital status, n (%)				2.618 (.106)
Married	44 (68.8)	19 (59.4)	25 (78.1)	
Not married	20 (31.3)	13 (40.6)	7 (21.9)	

Characteristic	Total (n = 64)	HF Patients (n = 32)	Healthy Adults (n = 32)	Chi-square or t-statistic (p-value)
Education				
Years, mean ± SD	15.9 ± 2.9	14.4 ± 2.5	17.3 ± 2.4	-4.69 (< .001)
HS or less, n (%)	15 (23.4)	12 (37.5)	3 (9.4)	7.053 (.008)
College Grad, n (%)	49 (76.6)	20 (62.5)	29 (90.6)	
LVEF, mean ± SD		25.9 ± 8.0		
NYHA class, n (%)				
II		20 (62.5)		
II-III		4 (12.5)		
III		8 (25.0)		
Charlson Comorbidity Index, mean ± SD		2.6 ± 1.2		
ICD, n (%)		29 (90.6)		
CRT (biventricular pacemaker), n (%)		13 (40.6)		
Dual or single chamber Pacemaker, n (%)		8 (25)		
DASI, mean ± SD	31.0 ± 18.7	16.6 ± 9.5	45.5 ± 13.5	-9.90 (< .001)
FCAS, mean ± SD	49.9 ± 9.0	47.2 ± 10.5	52.7 ± 6.2	-2.55 (.014)

Note. CRT = Cardiac Resynchronization Therapy; DASI = Duke Activity Status Index; FCAS = Florida Cognitive Activities Scale; HF = heart failure; ICD = Implantable cardioverter defibrillator: LVEF = left ventricular ejection fraction; NYHA = New York Heart Association

To further characterize the two groups, neuropsychological test scores were compared. The individual neuropsychological tests were first examined using partial correlation (controlling for age and education) to determine if relationships were present (see table 4.2). Using Cohen's guidelines (1992), all tests, except the COWA and figure memory recall ($r = -.013$; $p = .921$) and Digit Span and figure memory recall ($r = -.036$; $p = .784$), showed at least a small relationship with one another. The majority of the neuropsychological tests had small to moderate relationships ranging from $r = .133$ to $.434$ ($p = .302$ to $< .001$). A few neuropsychological tests, including the MMSE and the TMT Part B, ($r = -.512$; $p < .001$), the MMSE and the HVLT ($r = .505$; $p < .001$), and the MMSE and the HVLT DR ($r = .520$; $p < .001$); the TMT Part A and the TMT Part B ($r = .597$; $p < .001$); and the HVLT and the HVLT-DR ($r = .778$; $p < .001$), showed moderate to large relationships. Because some of the neuropsychological tests measured similar aspects of cognition (attention or executive function), some were subtests of the same measure, and some measured very different aspects of cognition (e.g. visuospatial memory and executive function), differing relationships among the tests were anticipated.

Table 4.2 Partial Correlation of Neuropsychological Tests with Age and Education Controlled (n = 64)

	MMSE	FC Total	FM Recall	CBT Total	Digit Span	TMT Part A	COWA Adjusted	TMT Part B	HVLT Total
FC Total	.355**							-	
FM Recall	.271*	.276*							.
CBT Total	.376**	.256*	.205						
Digit Span	.335**	.212	-.036	.390**					
TMT Part A	-.415**	-.143	-.273*	-.361**	-.309*				
COWA	.301*	.163	-.013	.133	.389**	-.269*			
TMT Part B	-.512**	-.279*	-.319*	-.434**	-.273*	.597**	-.170		
HVLT Total	.505**	.345**	.269*	.235	.298*	-.347**	.248	-.429**	
HVLT-DR	.520**	.267*	.310*	.161	.211	-.406**	.158	-.422**	.778**

Note. CBT = Corsi Block Tapping; COWA = Controlled Oral Word Association, adjusted score; FC = Figure Copy; FM = Figure Memory; HVLT = Hopkins Verbal Learning Test; HVLT-DR = Hopkins Verbal Learning Test-delayed recall; TMT = Trail Making Test; Higher scores are better on all neuropsychological tests except TMT in which lower scores are better; * $p < .05$ level; ** $p < .01$ level.

Characteristics of study variables: Neuropsychological tests. Previous studies (Alves et al., 2006; Beer et al., 2009; Callegari, et al., 2002; Elkadi et al., 2005; Pressler, Subramanian et al., 2010, Riegel et al., 2007 Trojano et al., 2003; Vogels, Oosterman, van Harten, Sheltens et al., 2007; Wolfe et al., 2006) have demonstrated worse mean neuropsychological test scores in HF patients when compared with healthy adults. Analyses were conducted on all neuropsychological test scores to determine if the scores were statistically different between the two groups. HF patients had worse cognition, indicated by p-values less than 0.05 for the comparison with healthy adults on most neuropsychological tests of visuospatial memory, attention, executive function, and short- and long-term memory (see table 4-3). Of particular note, two of the three visuospatial memory measures, figure copy test and figure memory recall test, although lower in the HF patients, were not significantly different between the groups ($t = -1.10, -1.88$; $p = .274, .065$, respectively). Scores on the third visuospatial measure, the Corsi Block-tapping task, were significantly worse in HF patients ($t = -2.44$; $p = .018$). When age and education were controlled, only scores on the TMT Part A were significantly different between HF patients and healthy adults.

Table 4.3 Neuropsychological Test Scores: Total Group, HF Patients, and Healthy Adults

Variable – mean (SD)	Total (n = 64)	HF (n = 32)	Healthy Adults (n = 32)	t-statistic (p-value)	F statistic (p-value)
Global Screening					
Mini-Mental State Exam	28.92 (1.24)	28.53 (1.4)	29.31 (1.0)	-2.64 (.011)	.207 (.651)
Visuospatial Memory					
Figure copy	9.48 (1.25)	9.31 (1.3)	9.66 (1.2)	-1.10 (.274)	.761 (.387)
Figure memory recall	8.55 (2.9)	7.88 (2.9)	9.22 (2.9)	-1.88 (.065)	.252 (.617)
CBT Test - backward	13.25 (3.3)	12.28 (3.2)	14.22 (3.1)	-2.44 (.018)	2.94 (.092)
Attention					
Digit Span-Scaled	10.59 (3.0)	9.72 (3.2)	11.47 (2.6)	-2.42 (.019)	2.251 (.139)
TMT Part A*	32.57 (14.2)	38.23 (15.1)	26.91 (10.7)	3.46 (.001)	4.901 (.031)
Executive Function					
Controlled Oral Word	43.83 (11.3)	40.16 (11.1)	47.5 (10.5)	-2.72 (.008)	1.101 (.298)
TMT Part B*	82.06 (63.9)	105.28 (78.3)	58.84 (32.5)	3.10 (.003)	1.719 (.195)
Short-term Memory					
HVLT	24.39 (5.2)	22.31 (4.8)	26.47 (4.7)	-3.50 (.001)	1.361 (.248)
Long-term Memory					
HVLT - DR	8.42 (3.0)	7.47 (3.0)	9.38 (2.8)	-2.63 (.011)	.215 (.645)

Note. CBT = Corsi Block-tapping; HF = heart failure; *Higher scores indicate worse performance; F statistic for ANCOVA, controlling age, gender, education

Analyses: Aims and Hypotheses

Aim 1: To compare allocentric spatial memory and learning, using a computerized software program, of older (over 55 years) HF patients and healthy adults of similar age. Data was obtained from the C-G Arena using two distinct methods for spatial memory and three distinct methods for spatial learning to determine if differences existed between HF patients and healthy adults. Quadrant time and heading error during the probe trial, described in Chapter III, Methods, was used to determine spatial memory. Path length, time, and heading error to target were used to determine spatial learning.

Hypothesis 1. The hypothesis that allocentric spatial memory performance was poorer in HF patients compared with healthy adults of similar age was tested during the probe trial. The amount of time spent in each of the four quadrants was determined for the HF patients and the healthy adults, and then the groups were compared using independent samples t-test. Next, heading error to the invisible target was calculated and the groups were compared with determine if differences were present. Hypothesis 1 was rejected based on the results of the analyses (See Table 4.4). Both groups spent a similar amount of time in the Northeast quadrant during the probe trial. The mean time spent in the target (Northeast) quadrant was shorter for the HF patients, however the difference between the groups was small and non-significant both when other variables were not controlled ($t = -.909$; $p = .367$) and when adjusted for age and gender ($F = 1.269$; $p = .264$). In addition, the mean heading error was worse in the HF patients compared with healthy adults; but again did not reach the level of significance ($F = .102$; $p = .751$).

Finally, using multivariate ANOVA and ANCOVA, adjusting for age and gender, quadrant time was examined to determine if the amount of time spent in each of the four quadrants differed significantly. A significant difference in quadrant time was detected with the greatest time spent in the Northeast (target) quadrant, Wilks' Lambda = .213, $F(3, 60) = 73.78$, $p < .001$. The effect size, computed as partial eta squared was .79 for quadrant time, which is quite large according to Cohen (1992). The difference in quadrant time between the two groups was not significant (Wilks' Lambda = .937, $F(3, 60) = 1.34$, $p = .271$; partial eta squared = .06); nor was it significant when controlled for age and gender (Wilks' Lambda = .931, $F(3, 58) = 1.433$, $p = .242$; partial eta squared = .07). This indicated that the participants in both groups learned the location of the target but spent similar time in each of the quadrants.

Table 4.4 Group Differences in Spatial Memory Performance During C-G Arena Probe Trial

Time Spent in Quadrant (measured in seconds)	HF Patients Mean (SD)	Healthy Adults Mean (SD)	Test Statistic (p-value)	Adjusted for Age & Gender
Northwest Quadrant	12.33 (12.61)	13.84 (18.83)	t = -.376 (.708)	F = .037 (.848)
*Northeast Quadrant	76.65 (28.83)	83.20 (28.78)	t = -.909 (.367)	F = 1.269 (.264)
Southeast Quadrant	19.91 (16.09)	16.93 (15.10)	t = .764 (.447)	F = .809 (.372)
Southwest Quadrant	11.14 (14.23)	6.07 (8.70)	t = 1.720 (.090)	F = 2.932 (.092)
Target Heading Error	43.00 (55.70)	41.84 (49.11)	t = .008 (.930)	F = .102 (.751)

Note. HF = heart failure; *Target was located in the Northeast Quadrant; Equal variance was assumed for all quadrants except the Southwest quadrant

Hypothesis 2. It was hypothesized that allocentric spatial learning, measured by six computerized learning trials, was poorer in HF patients compared with healthy adults of similar age. Three measures from the C-G Arena were used to test the hypothesis: path length, time, and heading error to target (explained in Chapter III, Methods). For all three measures, means for each of five learning trials on day one of testing and six trials on day two of testing, as well as the mean of all trials on each day, were analyzed (See tables 4.5 through 4.7). The first trial on day one was not included in analyses because the participants did not know the location of the target in trial one; thus day one trial one was considered an exploratory trial.

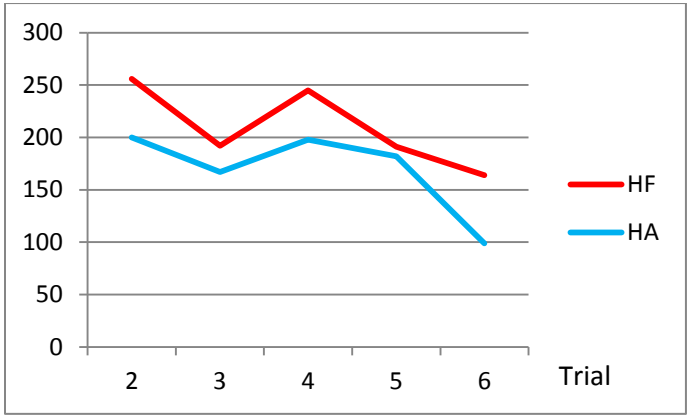
4.5 Comparison of Spatial Learning Using Path Length Across Learning Trials Between Groups

Total Path Length from Start to Target; measured in units		HF Patients Mean (SD)	Healthy Adults Mean (SD)	Multivariate Tests
Day One	Trial 2*	256.05 (223.91)	199.62 (184.34)	Group: Wilks' Lambda = .966
	Trial 3	191.66 (217.78)	167.19 (168.10)	F (4, 57) = .496; *p* = .739
	Trial 4	245.39 (285.45)	198.03 (222.95)	Partial Eta Squared = .03
	Trial 5	191.14 (220.22)	182.04 (193.48)	Age: Wilks' Lambda = .899
	Trial 6	164.21 (165.30)	99.48 (117.42)	F (4, 57) = 1.600; *p* = .187
				Partial Eta Squared = .10
				Gender: Wilks' Lambda = .939
				F (4, 57) = .928; *p* = .454
				Partial Eta Squared = .06
Day Two	Trial 1	211.87 (201.69)	137.84 (126.16)	Group: Wilks' Lambda = .888
	Trial 2	138.29 (216.96)	127.18 (174.69)	F (5, 56) = 1.408; *p* = .235
	Trial 3	160.46 (240.57)	93.76 (102.79)	Partial Eta Squared = .11
	Trial 4	135.80 (160.78)	104.72 (120.58)	Age: Wilks' Lambda = .923
	Trial 5	154.38 (216.57)	115.23 (175.08)	F (5, 56) = .928; *p* = .470
	Trial 6	112.90 (136.33)	157.46 (217. 70)	Partial Eta Squared = .08
				Gender: Wilks' Lambda = .957
				F (5, 56) = .499; *p* = .776
				Partial Eta Squared = .04

Note. HC = healthy control; HF = heart failure; Path length is in program units. *Trial one on day one was the learning trial and not included in analysis.

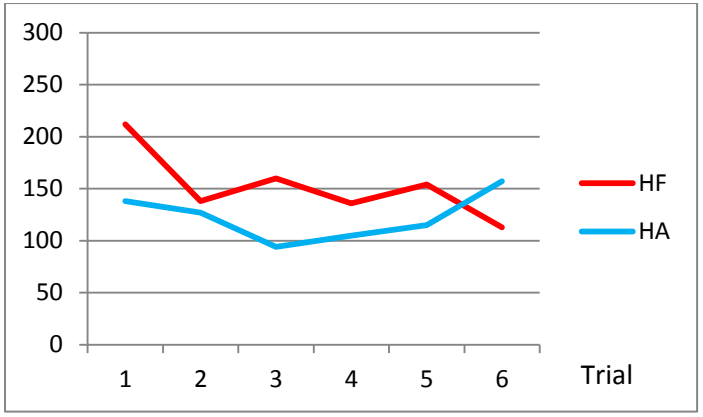
Path length by trial. Because Mauchly's test of sphericity indicated a significant difference in variance for repeated measures ANOVA (p = .043, p < .001; day one and day two, respectively), multivariate statistics were used to compare differences in path length. Levene's Test of Equality indicated equal variance could not be assumed for trial three on day two (p = .030), the remaining trials did not have significant F values (p = .111 - .712). As indicated in table 4.5, group was not a predictor of spatial learning using path length. The main effect for mean path length over time for the participants on day one was not significant (Wilks' Lambda = .883, F (4, 57) = 1.895, p = .124, Partial Eta Squared = .12) or on day two (Wilks' Lambda = .944, F (5, 56) = .664, p = .652, Partial Eta Squared = .06). Results of the analyses indicated that while, on average, participants improved path lengths to the invisible target significant learning did not occur. Figures 4.1 and 4.2 show mean learning path lengths from trial two through trial six on the day one (figure 4.1) and from trial one through trial six on the day two of testing (figure 4.2) for the HF patients and the healthy adults. As indicated by a longer path to the invisible target on the sixth trial compared with the preceding trials, the mean path lengths on day two, as illustrated on the graph, show that no learning occurred for the healthy adults.

Figure 4.1 Path Length to Target: Day One



Note. HA = healthy adult; HF = heart failure; Vertical Axis measured in program distance units; Trial 1, learning trial, not included in analysis

Figure 4.2 Path Length to Target: Day Two



Note. HA = healthy adult; HF = heart failure; Vertical Axis measured in program distance units

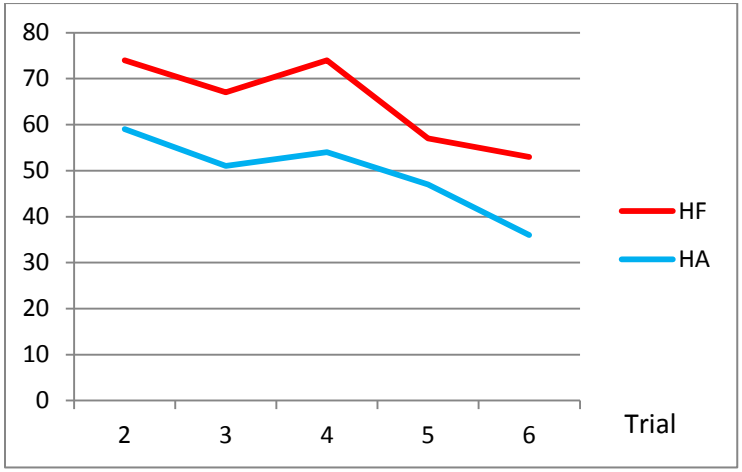
4.6 Comparison of Spatial Learning Using Time to Target Across Learning Trials Between Groups

Total Time from Start to Target; measured in seconds		HF Patients Mean (SD)	Healthy Adults Mean (SD)	Multivariate Tests
Day One	Trial 2	74.12 (51.53)	58.69 (55.94)	Group: Wilks' Lambda = .930
	Trial 3	67.05 (65.91)	50.87 (54.15)	F (4, 57) = 1.076; *p* = .377
	Trial 4	73.96 (72.23)	54.49 (62.27)	Partial Eta Squared = .07
	Trial 5	56.57 (62.81)	47.13 (50.24)	Age: Wilks' Lambda = .943
	Trial 6	53.22 (59.79)	35.52 (43.96)	F (4, 57) = .862; *p* = .492
				Partial Eta Squared = .06
				Gender: Wilks' Lambda = .937
				F (4, 57) = .965; *p* = .434
				Partial Eta Squared = .06
	Trial 1	62.57 (55.74)	49.22 (50. 50)	Group: Wilks' Lambda = .874
Day Two	Trial 2	38.56 (50.32)	43.61 (53.86)	F (5, 56) = 1.617; *p* = .171
	Trial 3	47.68 (56.53)	35.41 (46.65)	Partial Eta Squared = .13
	Trial 4	45.90 (53.44)	31.32 (58.68)	Age: Wilks' Lambda = .915
	Trial 5	44.04 (56.11)	40.38 (58.68)	F (5, 56) = 1.040; *p* = .403
	Trial 6	32.09 (43.34)	42.64 (57.21	Partial Eta Squared = .09
				Gender: Wilks' Lambda = .951
				F (5, 56) = .572; *p* = .721
				Partial Eta Squared = .05

Note. HF = heart failure; *Trial one on the day one was the learning trial and not included in analysis.

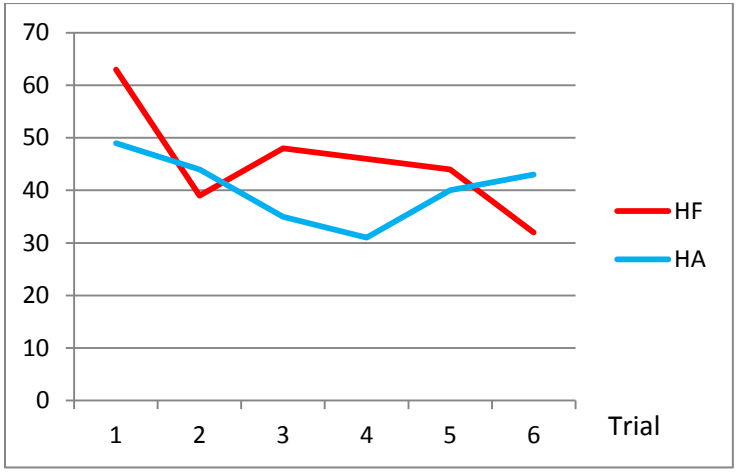
Time to Target by Trial. Because Mauchly's test of sphericity using repeated measures ANOVA indicated a significant difference in variance on second day of testing (p = .289, p = .017; day one and day two, respectively), multivariate rather than univariate statistics were used to analyze time to target. Levene's Test of Equality indicated equal variance could be assumed for all trials on day one and day two (p > .05). Neither group nor time to target had a significant effect on spatial learning as indicated in table 4-6. As noted in the time to target graphs (figures 4.3, 4.4), except for trials two and six on day two, it took longer for the HF patients to find the target, indicating worse performance. Time to target decreased over time from the first to the last trial during day one and two of testing for HF patients and healthy adults. However, the time to target differences between the groups did not reach the level of significance. Differences between the groups or among participants for time required to find the invisible target were not detected even when age and gender were controlled.

Figure 4.3 Time to Target - Day One



Note. HA = healthy adult; HF = heart failure; Vertical Axis measured in seconds; Trial 1, learning trial, not included in analysis

Figure 4.4 Time to Target - Day Two



Note. HA = healthy adult; HF = heart failure; Vertical Axis measured in seconds

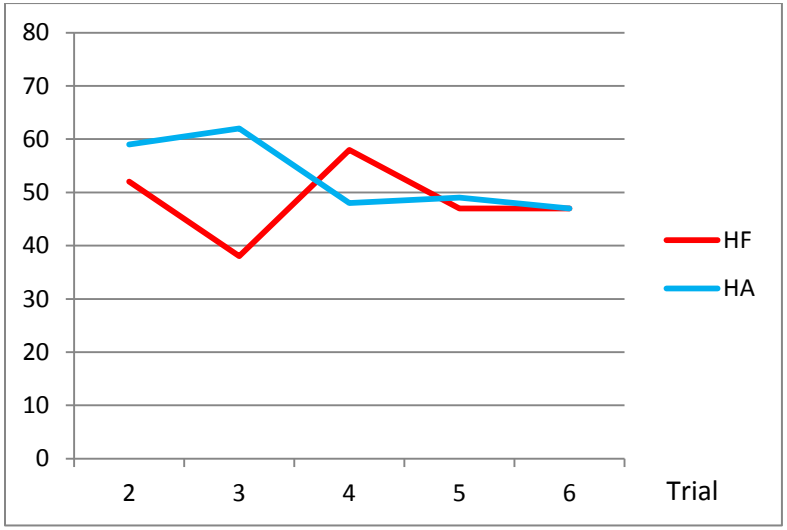
4.7 Comparison of Spatial Learning Using Heading Error Across Learning Trials Between Groups

Measured in degrees with higher scores indicating worse performance		HF Patients – Mean (SD)	Healthy Adults - Mean (SD)	Multivariate Tests
Day One	Trial 2	52.00 (51.353)	58.94 (48.473)	Group: Wilks' Lambda = .899
	Trial 3	38.09(42.847)	61.94(54.631)	F (4, 57) = 1.775; *p* = .147 .
	Trial 4	58.22(53.988)	48.06(51.299)	Partial Eta Squared = .11
	Trial 5	47.03(55.642)	49.38(47.161)	Age: Wilks' Lambda = .881
	Trial 6	47.06(49.594)	47.06(45.596)	F (4, 57) = 1.921; *p* = .119
				Partial Eta Squared = .12
				Gender: Wilks' Lambda = .975
				F (5, 57) = .364; *p* = .833
				Partial Eta Squared = .03
Day Two	Trial 1	78.58 (57.842)	56.84 (55.402)	Group: Wilks' Lambda = .903
	Trial 2	48.10 (45.403)	46.94 (55.110)	F (5, 54) = 1.154; *p* = .344
	Trial 3	47.55 (58.628)	34.52 (49.914)	Partial Eta Squared = .10
	Trial 4	52.26 (57.153)	27.77 (39.737)	Age: Wilks' Lambda = .919
	Trial 5	63.97 (59.574)	32.26 (41.003)	F (5, 54) = .951; *p* = .456
	Trial 6	53.32 (55.446)	46.74 (53.213)	Partial Eta Squared = .08
				Gender: Wilks' Lambda = .935
				F (5, 54) = .752; *p* = .588
				Partial Eta Squared = .07

Note. HF = heart failure

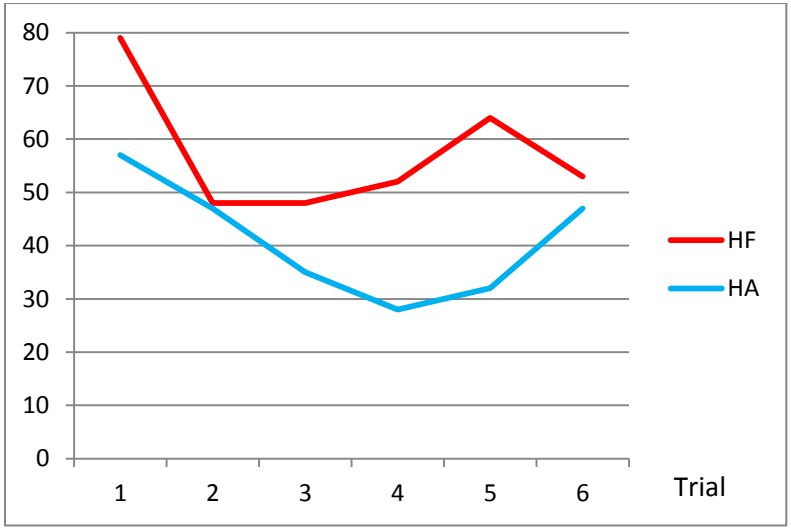
Heading Error to Target by Trial. Because Mauchly's test of sphericity indicated a significant difference in variance on the second day of testing using repeated measures ANOVA (p = .097, day one; p = .009, day two), multivariate rather than univariate statistics were used to compare differences in heading error. The change in heading error over time was not significantly different between the HF patients and the healthy adults on day one (Wilks' Lambda = .865; F (4, 57) = 2.220; *p* = .078; partial eta squared = .14; see table 7.4) or on day two (Wilks' Lambda = .937; F (5, 54) = .721; *p* = .611; partial eta squared = .06). No significant difference in heading error over time, as a measure of spatial learning, was evident for the five trials on day one and six trials on day two, or from group heading error for day one and day two, between HF patients and healthy adults. Figures 4.5 and 4.6, show mean heading errors for the day one and day two trials. Participants had small changes in heading error during day one of testing with HF patients performing better than healthy adults on the trial five and having the same mean score as healthy adults on trial six. During day two of testing, HF patients started with worse heading errors than the last trial on day one but demonstrated improved mean heading errors from the first to the last trial. Healthy adults had a smaller but similar increase in heading errors from the last trial on day one to the first trial on day two. This indicated that the majority of the participants did not remember the most direct path to the invisible target at the start of day two.

Figure 4.5 Heading Error - Day 1



Note. Higher scores worse; HA = healthy adult; HF = heart failure; Vertical Axis measured in degrees; Trial 1, exploratory trial, not included in analysis

Figure 4.6 Heading Error - Day 2



Note. Higher scores worse; HA = healthy adult; HF = heart failure; Vertical Axis measured in degrees

Mean Path Length, Time to Target, and Heading Error by Day. To further examine spatial learning of HF patients and healthy adults, mean scores were computed for all trials on day 1 and day 2 for each of the measures (path length, time to target, heading error). Independent-sample t-test was used to compare total mean spatial memory scores between HF patients and healthy adults (see table 4.8). Total mean scores for spatial learning measures were also compared using ANCOVA controlling for age and gender.

Table 4.8 ANCOVA for Comparison of Means for Measures of Spatial Memory (n = 64)

	HF Group Mean (SD)	Healthy Adult Group Mean (SD)	*t* Statistic (*p* value)	F Statistic (*p* value)	
Path length to target (units) Day One	223.67 (137.83)	168.55 (96.48)	1.854 (.069)	Gender Age Group	3.1 (.086) 1.7 (.203) 4.4 (.041)
Path length to target (units) Day Two	152.28 (133.72)	122.70 (100.70)	1.000 (.321)	Gender Age Group	2.2 (.146) 4.0 (.050) 1.3 (.253)
Time to Target (seconds) Day One	65.58 (43.17)	47.11 (30.85)	1.969 (.054)	Gender Age Group	4.7 (.033) 6.4 (.014) 5.3 (.025)
Time to Target (seconds) Day Two	45.14 (38.97)	40.43 (34.63)	.511 (.611)	Gender Age Group	9.1 (.004) 11.5 (.001) .9 (.336)
Heading Error Day One Higher score (degrees) = worse performance	48.48 (32.09)	53.08 (33.00)	-.565 (.574)	Gender Age Group	.3 (.604) 4.1 (.048) .5 (.496)
Heading Error Day Two Higher score (degrees) = worse performance	55.39 (33.50)	40.70 (33.19)	1.735 (.088)	Gender Age Group	1.8 (.183) .6 (.447) 3.5 (.067)

Note. HF = heart failure; F statistic for ANCOVA, controlling age, gender

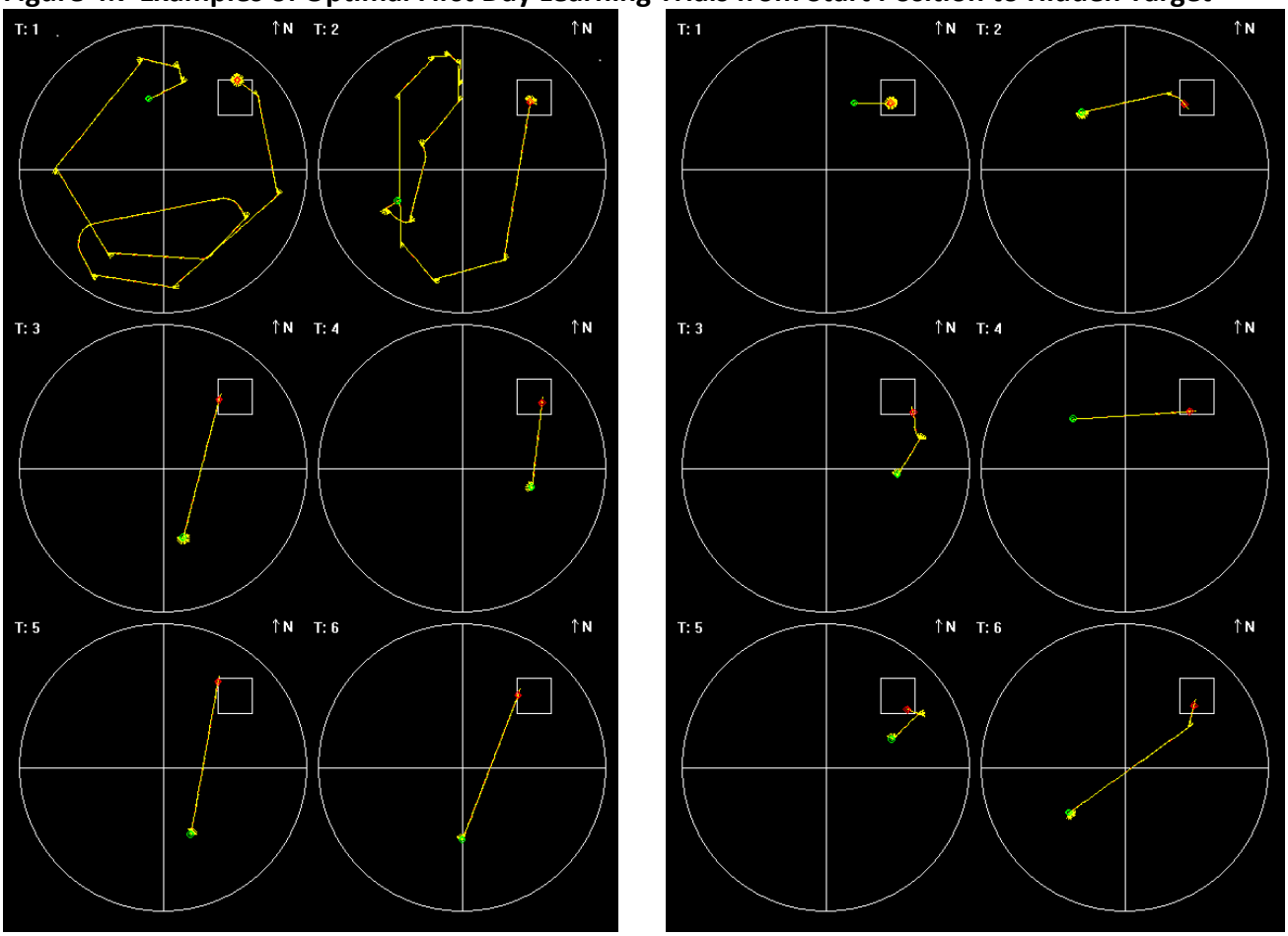
Mean scores for all trials on day one and day two showed that HF patients, on average, had worse spatial learning than healthy adults. These differences were less pronounced when age and gender were controlled (see table 4.8). Significant differences between the HF patients and healthy adults in path length and time to target on day one were found, controlling for age and gender. Age had a significant influence on time to target, day one and day two, and on heading error, day one. Gender had a significant influence on time to target, day one and day two.

Using repeated measures ANOVA for group, Hypothesis 2 was rejected. All measures (path length, time, and heading error to target) demonstrated improvement on days one and two of testing; however the improvement was not significant. When the means of the three measures (path length, time to target, heading error) were compared across the groups, the HF group had worse scores on all but heading error on the day one, however day one heading error did not reach the level of significance ($p = .496$). The HF patients did have significantly worse path length and time to target scores on day one when all trials were averaged ($p = .041$; .025; respectively).

Participants used a variety of techniques to find the invisible target; some followed the most direct path; others did not take a direct path but found the target relatively quickly; and some used large search areas that did not improve by shorter time or path length over time. Participants had no idea where the invisible target was in the first trial but the majority of participants (96%) found the invisible target. Figures 4.7 and 4.8 demonstrate actual paths individuals took on the day one of testing. The first drawing represents a straight path to the

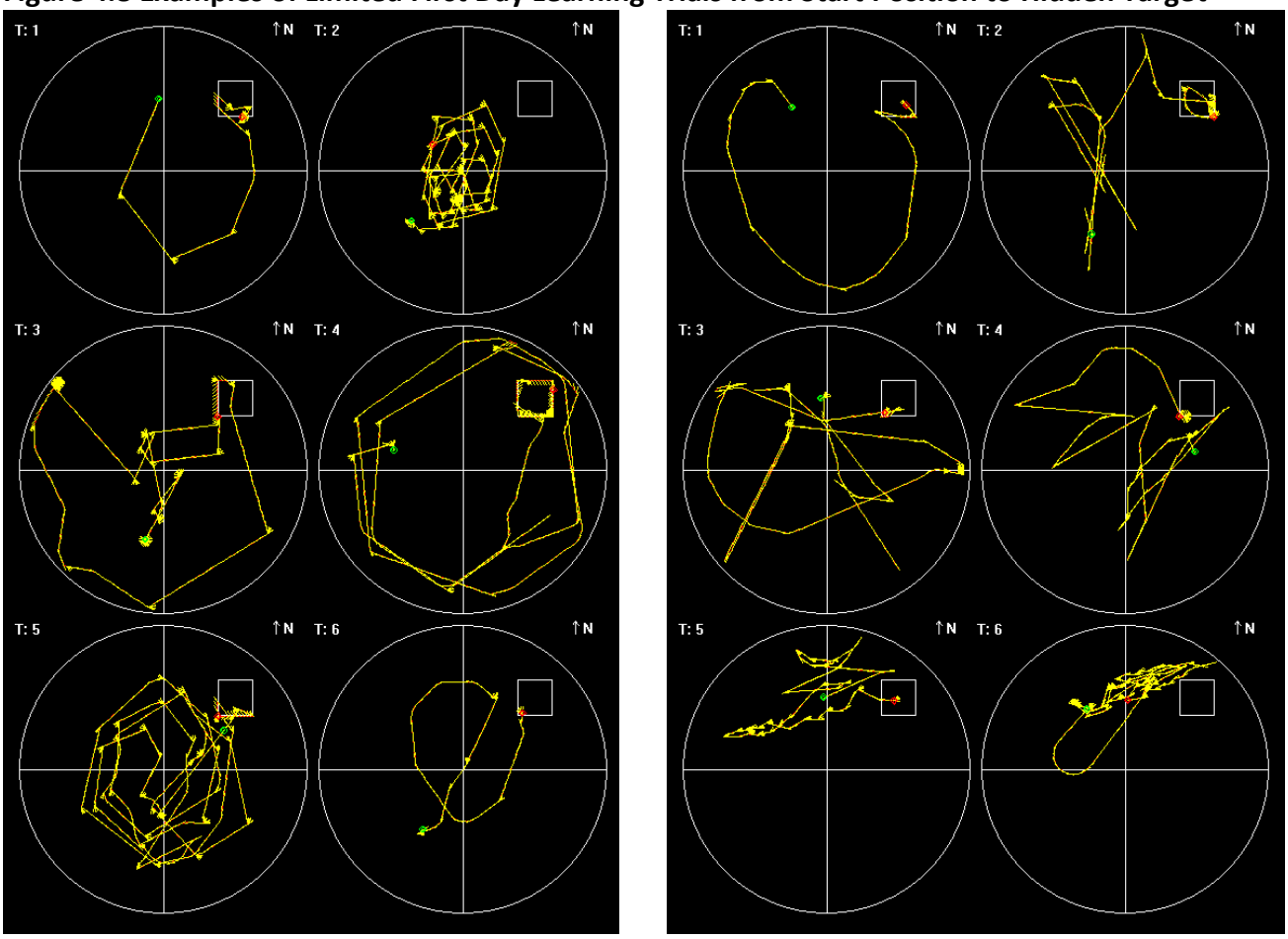
target on the last four trials and the second drawing represents an indirect path and a relatively large degree of heading error to the invisible target.

Figure 4.7 Examples of Optimal First Day Learning Trials from Start Position to Hidden Target



Drawing on the left is an example of a 65 year old male with HF who found the target quickly once the location was determined. Drawing on the right was a 62 year old female without HF who found the target quickly every time. Both of these drawings indicated good spatial learning. Top down view; Green dot, start location; Red dot end position; hidden target at the position of the small square in the upper right quadrant.

Figure 4.8 Examples of Limited First Day Learning Trials from Start Position to Hidden Target



Drawing on the left is a 59 year old male with HF. Drawing on the right is a 56 year old male without HF. Both of these drawings indicate adults who were not able to find the target more quickly and with less path length each subsequent trial. This indicated poor spatial learning.

Table 4.9 Change in Spatial Learning from Day One to Day Two

	HF – Mean (SD)		Healthy Adults – Mean (SD)		F Statistic (p-value)	
Path Length Difference	Day 1 – 6	164.2 (165.3)	Day 1 – 6	99.5 (117.5)	Age	11.3 (.001)
Last trial Day 1 – First Day 2	Day 2 – 1	211.9 (201.7)	Day 2 – 1	137.8 (126.2)	Gender	2.1 (.148)
					Group	4.8 (.032)
Time to Target	Day 1 – 6	53.2 (59.8)	Day 1 – 6	35.5 (44.0)	Age	14.3 (.000)
Last trial Day 1 – First Day 2	Day 2 – 1	62.6 (55.7)	Day 2 – 1	49.2 (50.5)	Gender	4.3 (.042)
					Group	2.5 (.123)
Heading Error to Target	Day 1 – 6	43.8 (46.8)	Day 1 – 6	47.06 (45.6)	Age	11.7 (.001)
Last trial Day 1 – First Day 2	Day 2 – 1	78.6 (57.8)	Day 2 – 1	60.28 (57.9)	Gender	.1 (.719)
					Group	.4 (.544)

Note. Day 1 - 6 = Day one, trial six; Day 2 - 1 = Day two, trial one; age and gender entered as covariates

Aim 2 - To determine the relationship between an allocentric virtual reality measure of spatial memory performance and egocentric paper and pencil measures of visuospatial memory in HF patients and healthy adults.

Hypothesis 3. The relationship between allocentric and egocentric measures of spatial memory and learning was investigated using partial correlation, controlling for age and education. Data were assessed for violations of assumptions of normality, linearity, and homoscedasticity. Allocentric spatial memory was measured using time spent in the target quadrant and heading error during the probe trial. Path length and time to target were measured during trial six on day two because it is not possible to measure time and path length to target when the target is removed (e.g. probe trial). Egocentric spatial memory was measured using the CERAD figure copy and figure memory recall and the Corsi Block-tapping backward and forward scores.

Table 4.10 Partial Correlation Between Allocentric and Egocentric Measures (n = 64).

	NE Quadrant	Path Length to Target	Time to Target	Heading Error to Target	Figure Copy	Figure Memory Recall	CBT Forward
Path Length to Target	-.494**						
Time to Target	-.462**	.944**					
Heading Error to Target	-.467**	.274*	.255*				
Figure Copy	.258*	.063	.118	-.021			
Figure Memory Recall	.090	.063	.099	.169	.276*		
CBT Forward	.282*	-.038	.006	-.139	.145	.179	
CBT Backward	.392**	-.223	-.247	-.395**	.307*	.187	.583**

Note. Age and education controlled; Path Length and Time to Target measured on trial six, day two; NE Quadrant and Heading Error to Target measured on trial seven, day two; CBT = Corsi Block-tapping; NE = Northeast; * $p < 0.05$ level; ** $p < 0.01$ level

A number of allocentric and egocentric measures were significantly correlated with each other (see table 4.10). There were small correlations (.145 to .307) among the different egocentric measures, except the Corsi Block-tapping forward and backward score (.583); this was expected because the forward and backward scores are subtests of the Corsi Block-tapping test. All of the allocentric subscores of spatial memory performance (C-G Arena) were significantly correlated with each other, controlling for age and education. The allocentric subscore measure correlations ranged from .255 to .944 ($p = .045$ to $< .001$). The subscores of time and path length to target, which are measuring very similar items, were very highly correlated (.944). Path length and time to target did not correlate significantly with egocentric measures of spatial memory. Time spent in the target quadrant during the probe trial had small correlations with figure copy and the Corsi Block-tapping forward and backward scores (.258, .282, .392, respectively). Heading error for the probe trial also had a small correlation with the Corsi Block-tapping backward score (-.395).

Aim 3 - Examine the influence of gender, group, perceived cognitive activity, and perceived functional capacity on spatial memory performance in older HF patients and healthy adults. Simultaneous multiple regressions were used to assess the ability of the independent variables, gender, group, perceived cognitive activity, and perceived functional capacity to describe the dependent variable, spatial memory performance as measured by time in the Northeast quadrant and heading error during probe trial. Due to the significant correlation between age and the dependent variable time spent in the Northeast quadrant during probe trial, age was entered into the regression for spatial memory performance.

Analyses were conducted to ensure the assumption for normality, linearity, multicollinearity, and homoscedasticity were not violated (see figures 4.9, 4.10). Multicollinearity, as indicated by Tolerance less than .01 (current study = 0.362 - .965) and Variance inflation factor (VIF) greater than 10 (current study = 1.037 – 2.759), was not present (Polit, 1996).

Figure 4.9 Normal Probability Plot and Scatterplot for Time Spent in Northeast Quadrant during Probe Trial

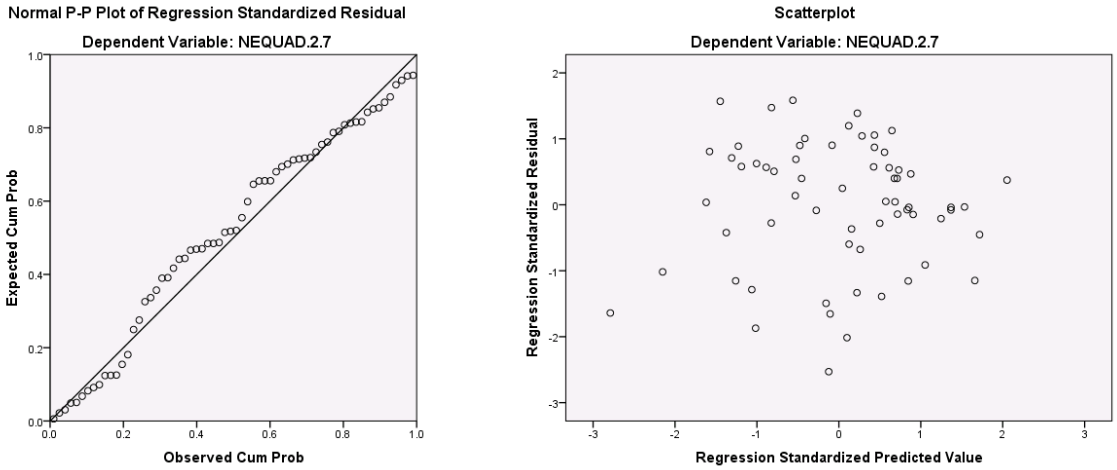
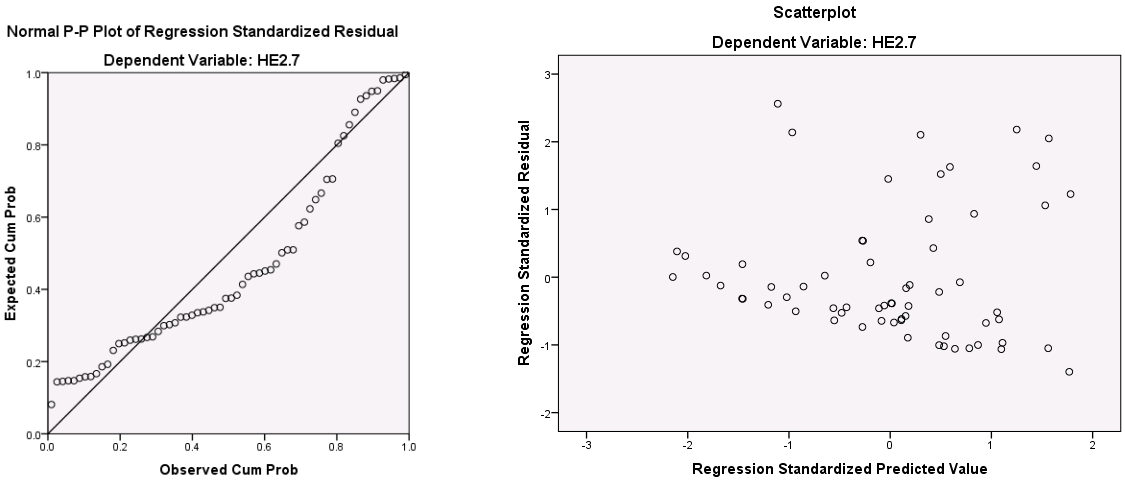


Figure 4.10 Normal Probability Plot and Scatterplot of Heading Error during Probe Testing



Correlation was moderate (r = -.491, $p < .001$) between time in Northeast quadrant and heading error during the probe trial for the HF patients and healthy adults, controlling for education. Time in the Northeast quadrant and age were moderately negatively correlated (r = -.364; p = .003). No other variables were significantly correlated (see table 4.11).

Table 4.11 Correlation Matrix for Model Predictors of Spatial Memory (n = 64)

	Time in Northeast Quadrant[a]	Heading Error[b]	FCAS	DASI
Heading Error	-.491**			
FCAS	-.051	.162		
DASI	.193	.091	.244	
Age	-.364**	.157	.121	-.096

Note. [a] = measured during probe trial in quadrant that contained the invisible target; [b] = during the probe trial; DASI = Duke Activity Status Index; FCAS = Florida Cognitive Activity Scale; **$p < 0.01$ level; * $p < 0.05$ level.

Simultaneous multiple regression are presented in Table 4.12 for both dependent variables (Time in Northeast quadrant, Heading Error; probe trial). For Northeast (target) quadrant during probe trial, after all variables were entered, the adjusted R^2 was .13, indicating 13% of the total variance for time spent in the was explained (F (5, 58) = 2.919, $p = .020$). The model for predicting spatial memory performance was statistically significant, with age being a significant independent predictor (see table 4.12).

For heading error to the target during probe trial, after all variables were entered, the adjusted R^2 was .04, indicating 4% of the total variance was explained (F (5, 58) = 1.566, $p =$ .184). The model did not predict spatial memory performance. Explanatory variables for probe

trial heading error were not significant independent predictors of spatial memory performance (see table 4.12).

Table 4.12 Multiple Linear Regression Model Explaining Spatial Memory Performance by Time in NE Quadrant and Heading Error During Probe Trial (n = 64)

		Unstandardized Coefficients		Standardized Coefficients	*t* (*p* value)
		B[a]	Standard Error[a]	Beta[b]	
Dependent variable: Time	(Constant)	136.742	35.233		3.881 (.000)
spent in the NE quadrant	Gender	11.726	7.078	.205	1.657 (.103)
	group	2.517	11.128	.044	.226 (.822)
	DASI	.337	.292	.218	1.153 (.254)
	FCAS Total	.023	.410	.007	.057 (.955)
Adjusted R^2 = .13	Age	-1.121	.396	-.338	-2.830 (.006)
Dependent variable:	(Constant)	-73.140	67.004		-1.092 (.280)
Heading error	Gender	-22.885	13.460	-.221	-1.700 (.094)
	Group	32.155	21.163	.311	1.519 (.134)
	DASI	.821	.555	.294	1.478 (.145)
	FCAS Total	.631	.779	.109	.810 (.422)
Adjusted R^2 = .04	Age	.804	.753	.134	1.067 (.290)

Note. DASI = Duke Activity Status Index; FCAS = Florida Cognitive Activity Scale; VIF = Variance inflation factor; [a] unstandardized; [b] standardized

Post-hoc Analyses

During the enrollment of healthy adults, every effort was made to match the ages of the HF patients. While the healthy participants were younger than the HF patients (mean age of 66.78 years versus 68.34 years) the difference between the two groups was not statistically significant ($t = .717$, $p = .476$). However, in the main analyses, age was a significant predictor for spatial memory and learning performance. Post-hoc analyses were conducted to more fully examine the influence of age on spatial memory and learning. After review of literature that divided adults into younger and older age groups; based on categories established by the Population Reference Bureau, the World Health Organization; and the spatial memory literature (Davis et al., 2008; Sanderson & Scherbov, 2008; World Health Organization, 2014), both groups were divided into age categories (<65 years, ≥65 years).

Spatial learning was analyzed using the group and age categories. Analysis of covariance was completed for path length, time, and heading error to target on the first and sixth trials of day two. Age group was entered as the comparison variable with gender and education entered as covariates. The significant differences among the four age-categorized groups, in general, were that younger HF and healthy participants performed better than older HF and healthy participants. An interesting and unexpected finding was that younger HF patients had significantly better scores than other age groups in many measures of spatial memory and learning, including path length and time to target (see table 4.12).

Table 4.13 Descriptives of Variables of Post-hoc Simultaneous Multiple Regression (n = 64)

Measures	Group	N	Mean	Standard Deviation	F statistic (*p*)
Path Length to First Target	1 Younger HF	12	92.16	51.46	5.83 (.001)
Day 2, Trial 1	2 Older HF	20	283.70	224.40	Differences found between 1
	3 Younger HA	17	138.19	129.21	& 2, 1 & 3
	4 Older HA	15	137.43	127.12	
Path Length to First Target	1 Younger HF	12	99.11	100.74	.70 (.557)
Day 2, Trial 6	2 Older HF	20	121.17	155.74	
	3 Younger HA	17	141.90	214.216	
	4 Older HA	15	175.10	227.75	
Time to First Target	1 Younger HF	12	24.39	16.39	5.13 (.003)
Day 2, Trial 1	2 Older HF	20	85.48	58.65	Differences found between 1
	3 Younger HA	17	45.00	52.47	& 2, 2 & 3
	4 Older HA	15	54.01	49.54	
Time to First Target	1 Younger HF	12	22.80	23.02	1.50 (.225)

Measures	Group	N	Mean	Standard Deviation	F statistic (*p*)
Day 2, Trial 6	2 Older HF	20	38.45	52.70	
	3 Younger HA	17	29.93	43.80	
	4 Older HA	15	61.23	70.32	
Heading Error	1 Younger HF	12	55.62	59.79	2.93 (.041)
Day 2, Trial 1	2 Older HF	19	95.17	51.83	Differences found between 2
	3 Younger HA	17	45.63	52.46	& 3
	4 Older HA	15	81.69	60.73	
Heading Error	1 Younger HF	12	71.46	52.73	1.57 (.207)
Day 2, Trial 6	2 Older HF	20	39.00	53.76	
	3 Younger HA	17	37.05	47.64	
	4 Older HA	14	62.08	59.91	

Note. HA = healthy adult; HF = heart failure; lower scores are better on all measures

Finally repeated measures ANOVA was completed for time and path length to target with gender as the comparison for group and age entered as a covariate. No significant differences were found between the groups (p = .511, p = .393, respectively).

Figure 4.11 Time to Target for Trials 2 – 6 on Day One

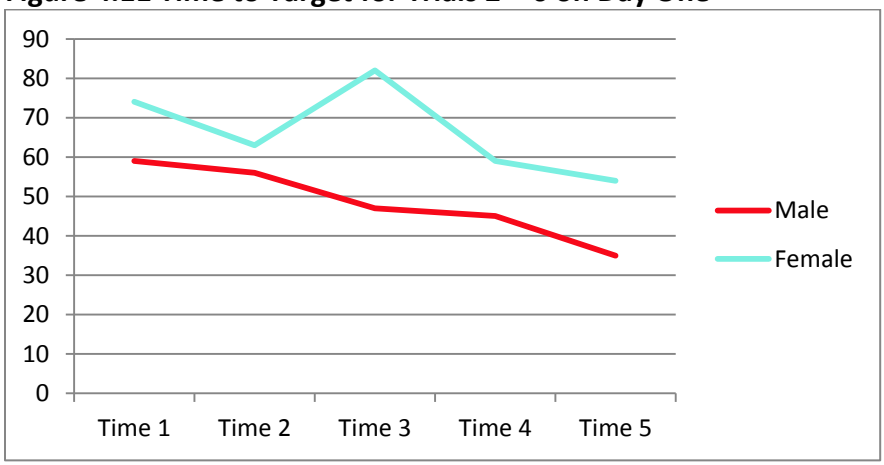


Figure 4.12 Path Length to Target for Trials 2 – 6 on Day One

Summary of Spatial Memory and Learning Analyses

Education level was significantly different between the HF patients and healthy adults but age and gender were not significantly different. Further, after controlling for education differences between the groups on neuropsychological test scores were not significant. No significant difference was found between HF patients and healthy adults for spatial memory or spatial learning measures. On further examination of spatial performance using mean learning scores, differences between the HF patients and healthy adults were significant. As hypothesized, significant partial correlation between the allocentric spatial measures was observed; however significant correlations between allocentric and egocentric spatial measures were also observed.

CHAPTER V

Discussion

The focus of chapter V is to discuss knowledge that was gained during the investigation of spatial memory and learning in HF patients and recommendations for future research in this novel field. The chapter is divided into three major themes including: specific aims and hypotheses of spatial ability and HF, strengths and limitations of the study, and implications for future research and nursing practice.

The study was initiated to examine spatial memory and learning in HF patients because many adults in the U. S. have HF, and currently, very little is known about spatial memory performance in HF patients. More specifically, it was conducted to determine if there were differences in spatial memory and learning between two groups of adults (HF patients and healthy adults) measured by an innovative virtual reality program, C-G Arena, developed to examine spatial memory and learning. Differences in spatial memory and learning using C-G Arena were evaluated to determine if group performance improved over time and whether there were differences in learning between the groups (HF patients and healthy adults). Allocentric (C-G Arena) and egocentric (figure copy, figure memory recall Corsi Block-tapping forward and backward) measures were compared to determine if scores were significantly correlated. And finally, explanatory variables of spatial memory performance were evaluated.

Specific Aims and Hypotheses of Spatial Memory and Learning and HF

This study is the first study to examine spatial memory in HF patients using C-G Arena, which is capable of measuring allocentric spatial memory. The HF patients had worse scores on measures of path length, time, and heading error to target, but these differences were non-significant when compared with healthy adults. Further, there was high variance in all of the measures of C-G Arena. Because the variance was high, learning trial scores were combined (mean score for path length, time, and heading error to target) and variance decreased; once variance was decreased HF patients had significantly worse measures of spatial learning, compared with healthy adults. Potential explanations for the initial, proposed, non-significant findings will be discussed below.

Aim 1: To compare allocentric spatial memory and learning, using a computerized software program, of HF patients with healthy adults. Aim 1 was the main objective in this study of spatial memory and learning in HF patients. It was hypothesized that there would be a difference between the groups mainly due to cerebral hypoperfusion and damage to the medial temporal lobe (including the hippocampus) that may occur in HF patients' memory during the probe trial using ANCOVA (controlling age, gender) and during learning trials using repeated measures ANCOVA (controlling age, gender). In this approach, hypotheses 1 and 2 were not supported and this lack of support may be due to at least five reasons.

First, lack of significant differences in spatial memory and learning may be because HF does not influence the development of spatial memory and learning dysfunction. This is an unlikely factor for the lack of significant differences between the two groups because previous research supports the progression of chronic cerebral hypoperfusion to hippocampal damage

and from hippocampal damage to spatial memory and learning dysfunction. Researchers (Cechetti et al., 2012; DeJong et al., 1999; Hai et al., 2009; Sun et al., 2010; Thong et al., 2013; Vicente et al., 2009) completed studies using an animal model with chronic cerebral hypoperfusion similar to mechanisms seen in HF and found significant differences between the groups in which rats with chronic cerebral hypoperfusion had worse spatial memory and learning than rats with similar surgery without chronic cerebral hypoperfusion. Further, previous research supported damage to areas of the brain responsible for spatial memory and learning in HF patients. Researchers in three different studies (Kumar et al., 2009; Woo et al., 2009; Woo et al., 2003) conducted neuroimaging studies in age-matched adults with and without HF; these researchers found significant differences in the HF group consistent with damage to brain structures responsible for spatial memory as compared with healthy adults. Researchers demonstrated differences in the medial temporal lobe, and specifically the hippocampus, with more damage in 13 HF patients when compared with age-matched healthy adults (Woo et al., 2009).

A second explanation may be because of the way C-G Arena was set up during the current study preparation. Participants were started in random locations to mimic the Morris Water maze and to encourage the use of allocentric spatial memory (Laurance et al., 2002). Further, the C-G Arena was set up for six trials on day one and seven trials on day two of testing to decrease HF patient burden. HF patients demonstrated worse spatial memory (probe trial ANCOVA) and learning (repeated measures ANCOVA), albeit non-significant. Variance was high in both groups and this may have been due to the random start and to six trials on day one and seven trials on day two. Having a random start for the participants was necessary to encourage

allocentric spatial memory but the program set the start locations and for some participants the start locations were very close to the invisible target while others had start locations that were further from the invisible target. The number of trials may not have been enough to demonstrate a learning curve. In order to decrease some of the variance, a mean score was determined for path, time, and heading error to target on day one and day two. The mean score decreased the variance and significant differences were found with HF patients having worse spatial memory using path length and time to target. These inconsistent differences in spatial memory and learning in the current study and significant differences in prior studies suggest the need for further investigation in HF patients and possibly further evaluation of the design and procedures used to conduct this study.

A third explanation for lack of significant differences between groups may be that HF patients in the current study were receiving optimal medical management at an academic medical center that possibly led to better cerebral blood flow and less spatial memory dysfunction. However, this explanation is unlikely because patients were symptomatic (NYHA class II or III) and had low LVEF at enrollment. Previous researchers who examined visuospatial memory for NYHA class II or III HF patients found significantly worse visuospatial scores in the HF patients compared with healthy age-matched adults (Alves et al., 2006; Beer et al., 2009; Callegari et al., 2002; Elkadi et al., 2005; Vogels, Oosterman, van Harten, Scheltens et al., 2007; Wolfe et al., 2006). While NYHA classification is a valid indicator of symptomatology, it may be beneficial in future studies to obtain a measurement of cerebral blood flow to provide a more accurate indication of the relationship between cerebral blood flow and spatial memory and learning.

A fourth explanation for non-significant findings in spatial memory and learning may be because the sample size was not large enough to detect differences. On average, the HF group spent less probe (absence of target, used to determine spatial memory) trial time in the quadrant where the hidden platform was placed during learning trials (worse performance) and had worse heading error than the healthy group; however, differences were non-significant. Learning trials tended to indicate worse performance in the HF group, however again the mean differences were small and non-significant. Sample size is a plausible consideration due to the lack of research completed in the area of spatial memory and learning to determine effect size of the measure. Effect size is generally estimated from the literature and in this study it could not be estimated from large-scale allocentric spatial performance but was instead based on small-scale visuospatial measures. Even still a power analysis was completed using the best values found in previous research for effect size and for the statistical analyses used in the current study.

Finally, a fifth explanation for non-significant differences between HF patients and healthy adults may be that age and gender influenced the relationship between spatial memory and learning and HF more than anticipated. In past studies, age and gender were considered to be contributing factors of spatial memory and learning. In the current study, age and gender were monitored during recruitment and were not significantly different between the groups. Age was an independent predictor for mean time to target. Older age was significantly correlated with worse egocentric spatial memory and learning (Byagowi & Moussavi, 2012; Iachini et al., 2009) but not with allocentric spatial memory and learning (Iachini et al., 2009). This may be due to the influence of age on the hippocampus. Age was significantly correlated

with many of the measures of spatial memory and learning. Age needs to be further examined in detail as a predictor variable of spatial memory in future studies with HF patients.

Gender was a significant covariate for time to target for mean scores of day one and day two testing with men demonstrating quicker (better) time. There is support in the literature that men as a group, have better allocentric spatial memory and learning compared with women (Astur et al., 1998; Canovas et al., 2008; Moffat et al., 1998; Rizk-Jackson et al., 2006; Tippett et al., 2009). Gender was not statistically different between participants with and without HF, although there were more women in the healthy group compared with women in the HF group. Gender was not a significant covariate for spatial memory or learning during ANCOVA of probe testing (memory trial) or during repeated measures ANCOVA testing (learning trials). In future studies it will be critical to include equal numbers of men and women with and without HF and a larger sample to have a better understanding of the relationship between gender and spatial memory and learning.

HF patients had significantly lower years of education; however, education was not a statistically significant covariate for memory (probe trial ANCOVA) or learning trials (repeated measures ANCOVA) using the C-G Arena. Further, education did not correlate with measures of spatial memory (heading error and time spent in target quadrant during probe testing). No studies were found that identified an effect of education on allocentric spatial memory.

Aim 2: To compare the allocentric and egocentric measures of spatial memory in all participants. It was proposed in hypothesis 3 that there would not be a significant correlation between the two different frames of reference (allocentric, egocentric) for spatial memory and learning measures; hypothesis 3 was supported. A non-significant correlation was found

between allocentric and egocentric measures, except between time in Northeast quadrant (allocentric), and figure copy, Corsi Block-tapping forward, and Corsi Block-tapping backward (egocentric), and between probe trial heading error (allocentric) and Corsi Block-tapping backward (egocentric) as noted in Chapter IV. Further supporting hypothesis 3, a lower percentage of allocentric and egocentric subscores were significantly correlated and had a lower magnitude than between allocentric subscores or between egocentric subscores. Non-significant correlations between allocentric and egocentric subscores were expected; however this was based on healthy adults because studies were not found in HF patients. In previous studies, researchers found lower correlations between allocentric and egocentric measures and higher correlations between subtests of allocentric measures (Laurance et al., 2002; Skelton et al., 2000). Unexpectedly, heading error (allocentric) and the Corsi block-tapping test (egocentric) had a significant negative correlation, possibly due to heading error demonstrating egocentric properties of spatial memory.

Visual inspection of the maps generated by the C-G arena software program indicated that approximately one-fourth of the participants were using an egocentric frame of reference to find the invisible target rather than an allocentric frame of reference. While determination of frame of reference was not part of the aims of the study, it may account for the higher correlation between the Corsi Block-tapping test (egocentric measure) and heading error (allocentric). Researchers (Bohbot et al., 2007) have demonstrated that adults use a different frame of reference depending on the situation. Egocentric navigation may require less cognitive demand as it does not require the development of a cognitive map. Navigating using a consistent route does not require an individual to attend to where they are going as carefully as

one would if in the process of developing a cognitive map of environmental relationships. In future studies, frame of reference should be addressed as part of the design of the study to further investigate this potentially important consideration.

The use of an egocentric frame of reference to navigate may explain the lack of differences found between the HF patients and healthy adults. Participants may use an egocentric frame of reference because it requires less cognitive demand, even though they were told they would be timed and should find the most direct path from start to where the invisible target was located. This may also be the reason why heading error had lower correlation coefficients with path length and time to find the invisible target. Even though participants tended to find the target more quickly as learning trials progressed, they continued to take the same path to the target, thus not reducing heading error. Iachini and colleagues (2009) found allocentric spatial memory did not change significantly over time but egocentric spatial memory worsened during the seventh decade in healthy adults. If age influences an egocentric but not an allocentric frame of reference, as Iachini and colleagues determined, it may help to explain why age had a significant influence on the different measures of spatial memory and learning in the current study; it may be that participants in general used an egocentric frame of reference for finding the invisible target.

Another interesting finding during the examination of relationships among egocentric measures was that figure memory recall was significantly correlated with figure copy but not with other egocentric visuospatial measures (CBT backward, CBT forward). Further analyses of neuropsychological tests showed figure memory recall and HVLT delayed recall (both

egocentric measures of long-term memory) were moderately correlated. Figure memory recall was also moderately correlated with TMT Part B (egocentric).

Aim 3: To examine the influence of gender, group, perceived cognitive activity, and perceived functional capacity on spatial memory performance. As hypothesized, gender, group, perceived cognitive activity, and perceived functional capacity predicted spatial memory as measured by time spent in the Northeast quadrant during the probe trial. The variables did not predict spatial memory as measured by heading error. Variables included in the model were supported by the theoretical and empirical literature to influence spatial memory but explanatory power was low. In multiple regression, age had a significant influence on path length, time to target, and time spent in the Northeast quadrant during probe testing, regardless of group. Age was the only variable that was an independent significant predictor of spatial memory and age has been a consistent predictor in previous studies (Carelli et al., 2011; Gordon et al., 2008; Moffat et al., 2001; Newman et al., 2000; Taillade et al., 2013). Explanatory variables (other than age) for spatial memory in this study were not supported. Even though age was similar between the groups, it had a significant influence on the outcome measures (spatial memory and learning). Age was a main result and requires careful consideration in future studies. Age will need to be carefully matched or stratified during study enrollment.

Gender was not a significant independent explanatory variable for spatial memory (full sample) in the current study. Further, there was not a significant difference for time and path length to target when men and women were compared; these non-significant gender differences were unexpected results. Researchers in previous studies found differences in path length and time to target, with men demonstrating better scores (Astur et al., 1998; Canovas et

al., 2008; Moffat et al., 1998; Rizk-Jackson et al., 2006; Tippett et al., 2009). In another study (Spiers et al., 2008), women had better spatial object-location memory and men had better mental rotation. The differences in these studies may be due to the frame of reference, possibly as a group, women tend to have better egocentric spatial memory and men tend to have better allocentric spatial memory (Astur et al., 1998; Canovas et al., 2008; Tippett et al., 2009; Pressler, Subramanian, et al., 2010). Support was also found in the HF literature in a study in which men had worse egocentric visuospatial memory (figure memory recall) when compared with women (Pressler, Subramanian, et al., 2010). Future research should include an equal number of men and women within the groups and a larger sample size.

Perceived functional capacity as measured by the DASI was significantly different between the two groups (HF patients, healthy adults) and this is due to the presence of HF. In the regression model, perceived functional capacity was not a significant predictor of spatial memory. The DASI has demonstrated reliability and has been validated for measuring perceived functional capacity (dressing, walking, household chores, etc.) in HF patients, however it did not distinguish which participants would have worse spatial memory and as such does not support further use of the DASI as a predictor of spatial memory in HF patients. It may be helpful to include an objective measure of physical activity in future studies to determine if more physical activity is correlated with better spatial memory.

Perceived cognitive activity as measured by the FCAS was significantly different between HF patients and healthy adults with the HF patients having lower perceived cognitive activity. However, the FCAS was not a significant predictor of spatial memory performance. It was anticipated that the FCAS would approximate cognitive activity levels of the participants but it

is very possible that perceived cognitive activity and actual cognitive activity levels do not have the same influence on spatial memory. Another reason why the FCAS was not a significant independent predictor of spatial memory could be that cognitive and social activities in humans may not be a mechanism for maintaining or improving spatial memory. It was acknowledged during study design that perceived cognitive activities of participants in the current study were different from controlling cognitive activities in past animal studies. The FCAS measures perceived cognitive activity and previous studies created an environment with an enhanced level of cognitive activities; these are not quantifying the same ability. The influence of cognitive, social, and physical activities on spatial memory needs to be further examined in future research studies using valid, reliable measures focused on actual rather than perceived activities.

There may be other unknown reasons why the variables were not able to more fully predict an individual's spatial memory ability. A major consideration was discussed in Chapter I and may be due to limited research in the area of how best to measure spatial memory and learning performance. The C-G Arena was developed to measure spatial memory; it was anticipated that participants would use allocentric spatial memory but approximately 25% were most likely using egocentric spatial memory. While an egocentric frame of reference may be useful for finding an invisible target, it may not be as useful when trying to remember where one has placed belongings or for preventing an individual from getting lost during the performance of daily activities. Brain structures were found to be more or less active depending on the frame of reference with more activity in the hippocampus during allocentric tasks and more activity in the caudate nucleus during egocentric spatial memory tasks suggesting the

hippocampus is responsible for allocentric spatial memory (Bohbot et al, 2007). Egocentric memory performance was found to worsen in older age while allocentric memory performance did not change with age (Iachini et al., 2009). Frame of reference (egocentric versus allocentric) may have influenced the ability of the measure to predict spatial memory.

Due to the low explanatory power of the simultaneous regression model for time spent in the Northeast quadrant, it is likely that variables exist that were not identified during the review of the literature that may have a major influence on spatial memory. It may be that some adults have developed a higher level of allocentric spatial memory over their lifespan because of experience with navigation or possibly due to a genetic predisposition. It is possible that examining spatial memory and learning in a longitudinal study might provide more information about whether HF decreases the ability to navigate.

Strengths and Limitations of the Study

Major Strengths of the Current Study

The current study was one of the first to use a novel large-scale virtual reality software program (C-G Arena) to measure allocentric spatial memory and learning in HF patients. In the HF literature review, no publications were found in which researchers used measures in which participants could use allocentric spatial navigation. Further, the current study measured spatial learning by using recurrent trials of navigation over two days of testing. Most researchers in the HF literature examined egocentric visuospatial memory using a egocentric measure completed at one point in time (Alves et al., 2006; Beer et al., 2009; Callegari et al., 2002; Elkadi et al., 2005; Pressler, Subramanian et al., 2010; Riegel et al., 2002; Trojano et al., 2003; Vogels,

Oosterman, van Harten, Scheltens et al., 2007; Wolfe et al., 2006). While these studies were able to determine visuospatial memory, the ability to demonstrate learning was not possible.

Examination of cognitive, social, and physical activities as factors that may be neuroprotective in HF and may influence spatial memory was an important aspect of this study. Researchers (Briones et al., 2004; Briones et al., 2000; Cechetti et al., 2012; Zhu et al., 2011) conducting animal studies have demonstrated that increasing cognitive activities in the form of novel toys, socialization with other animals, and having access to physical activities improved spatial memory and learning performance. Neuroplasticity was demonstrated in these animal studies and it is important to determine if this is possible in humans and if so; how best to intervene to improve daily functional abilities. It may be possible to improve spatial memory through cognitive training and this may have a protective mechanism. It was found in a relatively recent study that spatial ability was improved in brain-lesioned patients after passive navigation training using virtual reality (Kober et al., 2013). Further, allocentric spatial memory performance was correlated with increased gray matter in the hippocampus of healthy older adults (60-75 years; Konishi & Bohbot, 2013).

Limitations of the Study

A limitation of this study was the small sample size. A power analysis was completed for the study aims prior to beginning the current study but lack of research on allocentric spatial memory and learning in HF patients may have led to an imprecise effect size. Another limitation was that lack of research on allocentric spatial memory and learning in patients with HF made it difficult to determine specific predictor variables, specific to navigation. A possible limitation was due to significantly different levels of education between the HF patients and healthy

adults. While education was not found to be significant in analyses, it may have influenced spatial memory and learning to some degree.

Implications for Future Research and Nursing Practice

Research has demonstrated relationships between brain pathology and HF, and between brain pathology and spatial memory and learning. The relationship between HF and spatial memory and learning is still not clear nor is the understanding of how best to measure spatial memory and learning in HF patients. Much of the evidence seems to point to hypoperfusion of the brain ultimately affecting the hippocampus. Importantly, visuospatial memory has been identified as an independent predictor for mortality in HF patients (Pressler, Kim et al., 2010).

This study demonstrated support that compared to healthy adults, HF patients had poorer spatial memory and learning. The study confirmed a relationship between spatial memory and learning, and age. The current study validated that there are significant gaps in what explains spatial memory and learning. There are issues with current measures. Further, there needs to be a better understanding of which factors need to be considered as important moderators or mediators between HF and spatial memory and learning.

Researchers need to continue to examine which variables are influencing the relationship between HF and spatial memory and learning. Future research should be conducted that minimally includes a valid, quantitative measure of past allocentric spatial memory and learning. Virtual reality, including the C-G Arena, as a measure of allocentric spatial memory and learning should be assessed for validity and reliability in HF patients and with other allocentric measures. Ultimately, a longitudinal study should be conducted with

patients identified as being at risk for HF without active disease to include repeated, valid, reliable measures of allocentric and egocentric spatial memory and learning.

Benefits of this study included an increased understanding of factors that influence spatial memory and learning. This study was developed to provide a basis for possible development of nursing and public health interventions directed toward improving a patient's ability to navigate. The knowledge that was gained in this study will facilitate future studies to improve the ability to measure spatial memory and learning in HF patients and to identify variables that may better predict better navigational skills. The ultimate aim is to use the knowledge gained in this study to develop and evaluate interventions and eventually to develop clinical practice guidelines generated from evidence-based practice. Use of evidence-based practice guidelines may improve the daily functional abilities of this growing segment of the population.

HF is a significant problem in the U. S. and is predicted to continue to affect more adults. Visuospatial memory may be an important consideration of mortality for HF patients. HF patients, especially those over 65 years, need to be assessed for their ability to complete independent activities of daily living that involve spatial memory performance including driving, medication preparation, and management of important instructions for self-care. Family involvement in patient care should be assessed to evaluate if HF patients are receiving necessary assistance. We as nurses need to be ready to further the science and to disseminate knowledge about this vital area of research.

Conclusion

In conclusion, HF patients had worse spatial memory and learning compared with healthy adults when variance was decreased. Allocentric and egocentric measures of spatial memory have distinct properties and this should be considered in study design. Older age was a predictor of spatial memory performance in HF patients and healthy adults. Age is a known predictor but it may be related to an egocentric rather than an allocentric frame of reference. Future studies need to focus on other predictors of allocentric spatial memory.

Appendix A: Procedures for Spatial Memory and HF Study

1. Potential patients will be enrolled either through PI's previous study contacts of HF patients or as identified by Dr. Koelling or his designee and contacted by the PI
2. Potential participants will be enrolled either as a contact through eligible patients (relative/friend) or from flyers for healthy older (over 55 years) participants placed within the medical center or on the UM campus per policy
3. During initial contact with patients/healthy adults:
    a. Objectives and specific aims will be verbalized to all participants
    b. Inclusion and exclusion criteria will be verified
    c. Ability to maintain uninterrupted, quiet environment will be ascertained
    d. Two visits on consecutive days will be scheduled

First Visit

1. Read the informed consent statement to the participant, answer questions, and witness signature of participant (25 minutes)
2. Screen participant using the MMSE (5 minutes) and Snellen eye chart (5 minutes)
    a. Score ≥ 24 continue with testing
    b. score < 24 - explain to participant that study inclusion criteria requires score to be 24 or over
    c. 20/40 or better with corrective lenses to continue with testing
3. Prior to testing, facilitate proper environment including:
    a. Turn off home and cell phone ringers; answering machine volume off
    b. Television and radios off

c. Instruct family members that testing cannot be interrupted once started

d. Encourage bathroom use prior to beginning testing

e. All questions to be read to participant by examiner

4. Provide instructions to participant about testing procedure for C-G Arena and answer questions about the procedure (5 minutes)
5. Participant will be given a 5-minute practice session to learn how to use joystick and practice finding a visible platform (5 minutes)
6. Conduct C-G Arena testing session (23 minutes)
    a. Participant will complete six 3-minute trials to learn the location of the hidden platform
    b. Allow a 1-minute rest period between each trial
7. Following a 5-minute break complete alternating schedule of study forms and neuropsychological testing (see Table 1). (25 minutes)

Table 1. Alternating Schedule of Forms for First Day Following C-G Arena Learning Trials

First Visit Schedule A	First Visit Schedule B	First Visit Schedule C
DASI	FCAS	Demographics
FCAS	Demographics	DASI
Demographics	DASI	FCAS

8. Thank the participant for their time and confirm time for testing on the following day

Second Visit

1. Prior to testing, facilitate proper environment including:

a. Turn off home and cell phone ringers; answering machine volume off
b. Television and radios off
c. Instruct family members that testing cannot be interrupted once started
d. Encourage bathroom use prior to beginning testing
e. All questions to be read to participant by examiner

2. Set up computer and conduct C-G Arena learning phase of 6 trials (23 minutes) followed by probe testing (5 minutes)
    a. Participant will have 6 3-minute trials to find the hidden platform with a 1-minute break between the trials
    b. Platform will be removed following the learning phase
    c. Participant will have 2 minutes to search for the hidden platform after platform has been removed
    d. Inform participant after probe trial that platform was removed to determine the time that would be spent in the vicinity of the platform to determine extent of memory for platform location
3. Finish neuropsychological testing according to alternative schedule per table 2 (80 minutes testing and 5 minute break)

Table 2. Alternating Schedule of Tests for Second Day Following C-G Arena Learning Trials

Second Visit Schedule A	Second Visit Schedule B	Second Visit Schedule C
CERAD	HVLT-R	CERAD
HVLT-R	CERAD	HVLT-R

Corsi	Corsi	Corsi
Break	**Break**	**Break**
COWA	COWA	Digit Span
Digit Span	TMT-A	COWA
TMT-A	TMT-B	TMT-A
TMT-B	Digit Span	TMT-B

4. Give the participant the gift-card incentive

5. Thank the participant for agreeing to take part in the study

Appendix B: Patient Interview Form

Personal information

a. Age (DOB): _____

b. Gender: (1) ❑ Woman (2) ❑ Man

c. Ethnicity:(1) ❑ Hispanic or Latino (2) ❑ Non-Hispanic or Latino (3) ❑ Unknown

d. Race: (1) ❑ American Indian/Alaskan Native (2) ❑ Asian (3) ❑ Native Hawaiian or other Pacific Islander (4) ❑ Black or African American (5) ❑ White (6) ❑ Multi racial (7) ❑ Unknown

e. Marital Status: (1) ❑ Married (2) ❑ Not married

f. What level of education have you completed? _____ (high school/GED =12, associate=14, Bachelor=16, Master 18, JD=19, Doctorate/MD=20)

g. What is the actual number of years you have completed in school? _____

h. Employment status: (1) ❑ employed (2) ❑ unemployed (2) ❑ retired

i. Your occupation: _____ (previous occupation if retired)

j. Do you live alone? (1) ❑ Yes (2) ❑ No

1. If "No", who do you live with? (1) ❑ spouse/partner (2) ❑ children (3) ❑ friend (4) ❑ Other relative (5) ❑ other

k. Handedness: (1) ❑ Right handed (2) ❑ Left handed

Health History

l. Height _____ Feet _____ Inches

m. Weight _____ Pounds

n. Smoking history:

1. Do you currently smoke? (1) ❑ Yes (2) ❑ No

2. If no, have you ever smoked? (1) ❑ Yes (2)

❑ No

3. How many years have (did) you smoked (smoke)? _____

4. How many packs a day do (did) you smoke? _____

5. When did you quit smoking?

_____

6. Calculated pack years.

_____

7. Do you use other tobacco?

(1) ❑ Yes (2) ❑ No

8. If yes, which do you use? (1) ❑ pipe (2) ❑ cigar (3) ❑ chewing tobacco (4) ❑ other

9. How much do you smoke (chew) a day?

_____

10. Do you drink alcohol?

_____

a. If yes, how much do you drink

_____

Medication

11. Do you currently take prescribed medications? (1)

❑ Yes (2) ❑ No

a. If yes, did you take all of your medications as prescribed today? (1) ❑ Yes (2) ❑No

b. If "No", which medications did you not take as prescribed? _____

Menstrual history (Female only):

12. Have you ever taken hormone replacement therapy? (1) ❑

Yes (2) ❑ No

a. If "Yes", for how long?

_____

b. If "Yes", when did you stop taking?

_____

Appendix C

New York Association (NYHA) Functional Classification

This scale assists in the determination of functional ability in patients with cardiac disease.

Class I	Patients with cardiac disease, but without resulting limitation of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, dyspnea, or anginal pain.
Class II	Patients with cardiac disease resulting in slight limitation of physical activity. They are comfortable at rest. Ordinary physical activity results in fatigue, palpitation, dyspnea or anginal pain.
Class III	Patients with marked limitation of physical activity. They are comfortable at rest. Less than ordinary activity causes fatigue, palpitation, dyspnea, or anginal pain.
Class IV	Patients with cardiac disease resulting in inability to carry on any physical activity without discomfort. Symptoms of heart failure or of the anginal syndrome may be present even at rest. If any physical activity is undertaken, discomfort is increased.

Appendix D: Duke Activity Status Index

Now I am going to ask you about some activities that people do. Please tell me if you can do these things. The responses are:

1 = Yes, with no difficulty

2 = Yes, with some difficulty

3 = No, I can't do this

4 = I don't do this for other reasons

Can you….

1. Take care of yourself, that is, eating, dressing, bathing, and using the toilet?	1	2	3	4
2. Walk indoors, such as around your house?	1	2	3	4
3. Walk a block or two on level ground?	1	2	3	4
4. Climb a flight of stairs or walk up a hill?	1	2	3	4
5. Run a short distance?	1	2	3	4
6. Do light work around the house like dusting or washing dishes?	1	2	3	4
7. Do moderate work around the house like vacuuming, sweeping floors, carrying in groceries?	1	2	3	4
8. Do heavy work around the house like scrubbing floors, or lifting or moving heavy furniture?	1	2	3	4
9. Do yard work like raking leaves, weeding or pushing a power mower?	1	2	3	4

10. Have sexual relations?	1	2	3	4
11. Participate in moderate recreational activities, like golf, bowling, dancing, double tennis, or throwing baseball or football?	1	2	3	4
12. Participate in strenuous sports like swimming, single tennis, football, and basketball or skiing?	1	2	3	4

Total Score_____

Appendix E: Trail Making Test (TMT) Parts A & B

Instructions:

Both parts of the Trail Making Test consist of 25 circles distributed over a sheet of paper. In Part A, the circles are numbered 1 – 25, and the patient should draw lines to connect the numbers in ascending order. In Part B, the circles include both numbers (1 – 13) and letters (A – L); as in Part A, the patient draws lines to connect the circles in an ascending pattern, but with the added task of alternating between the numbers and letters (i.e., 1-A-2-B-3-C, etc.). The patient should be instructed to connect the circles as quickly as possible, without lifting the pen or pencil from the paper. Time the patient as he or she connects the "trail." If the patient makes an error, point it out immediately and allow the patient to correct it. Errors affect the patient's score only in that the correction of errors is included in the completion time for the task. It is unnecessary to continue the test if the patient has not completed both parts after five minutes have elapsed.

Step 1: Give the patient a copy of the Trail Making Test Part A worksheet and a pen or pencil.

Step 2: Demonstrate the test to the patient using the sample sheet (Trail Making Part A – *SAMPLE*).

Step 3: Time the patient as he or she follows the “trail” made by the numbers on the test.

Step 4: Record the time.

Step 5: Repeat the procedure for Trail Making Test Part B.

Scoring:

Results for both TMT A and B are reported as the number of seconds required to complete the task; therefore, higher scores reveal greater impairment.

Average Deficient Rule of Thumb

Trail A 29 seconds > 78 seconds Most in 90 seconds

Trail B 75 seconds > 273 seconds Most in 3 minutes

Sources:

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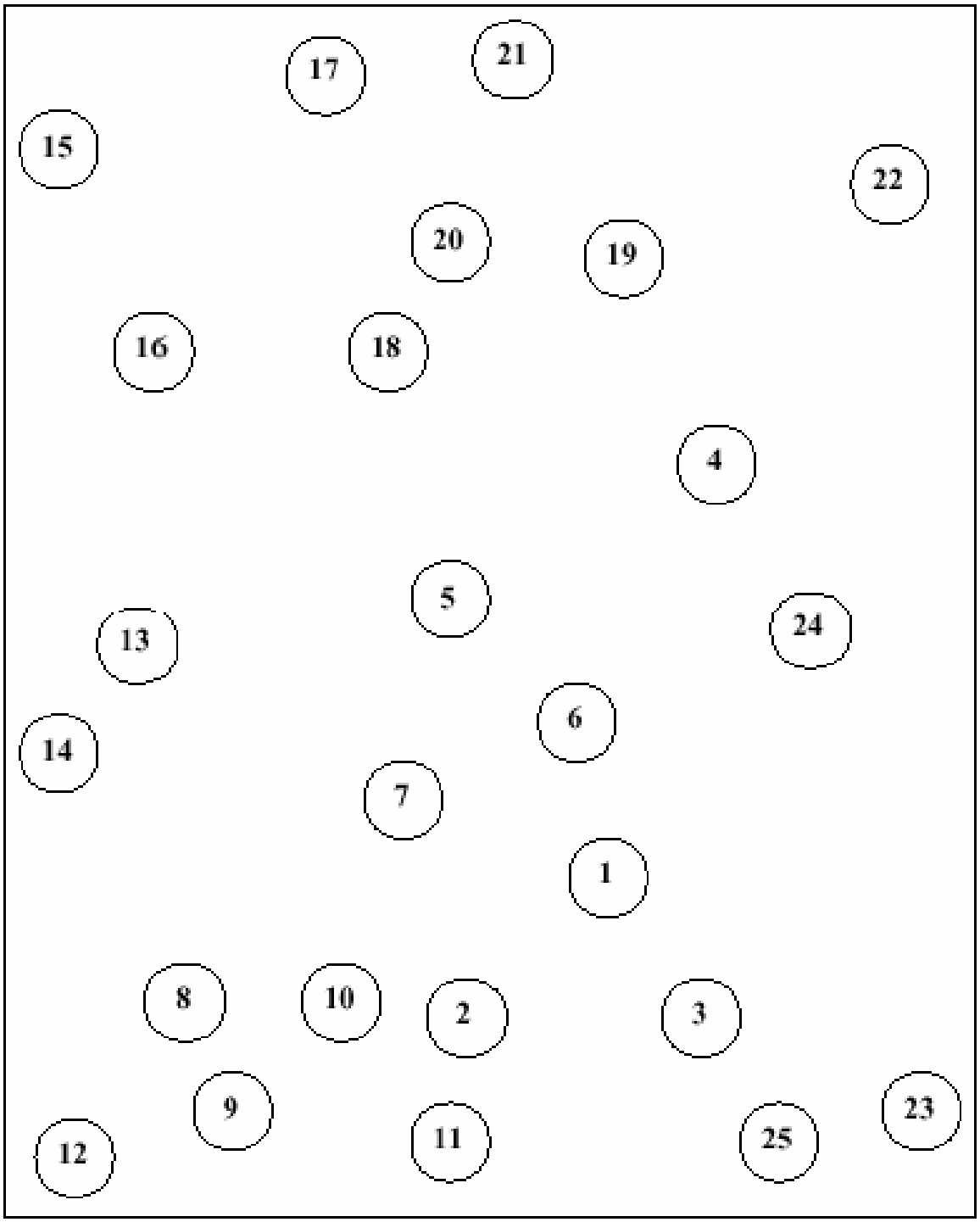
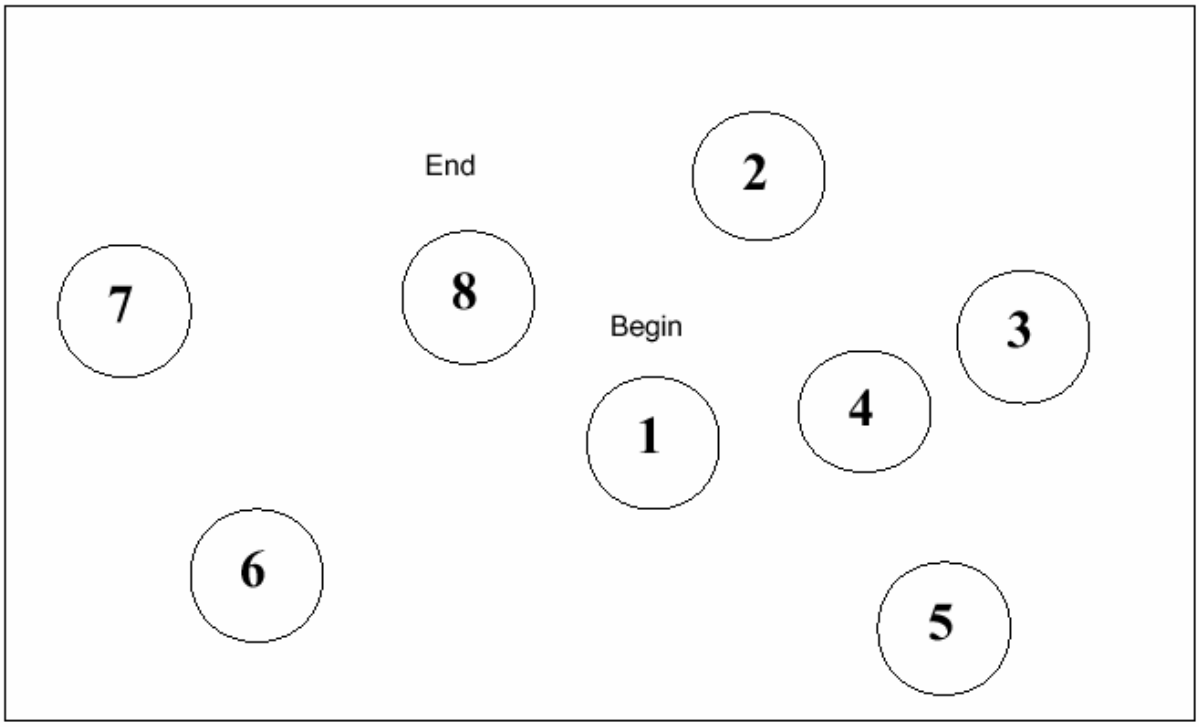
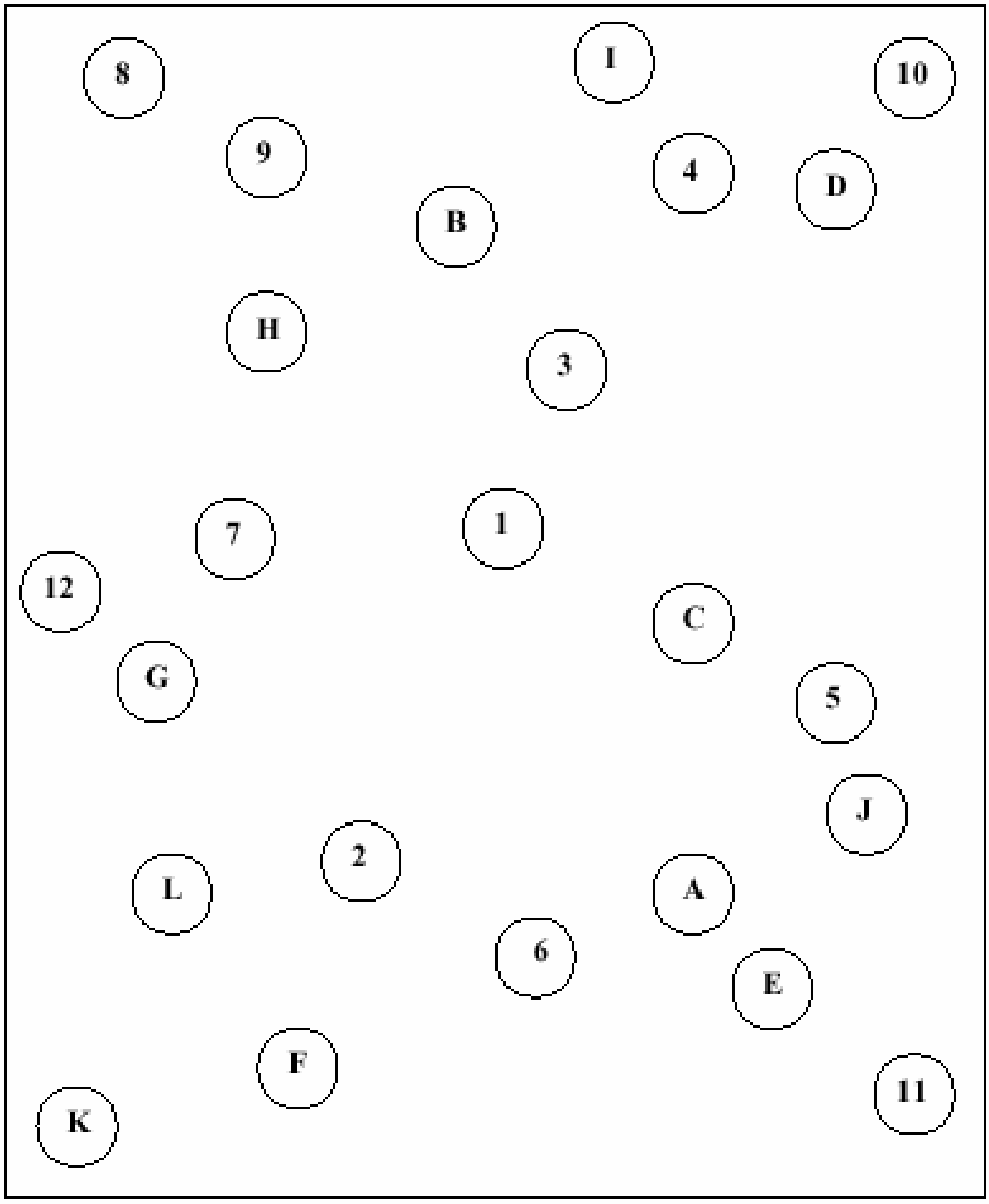
Trail Making Test Part A



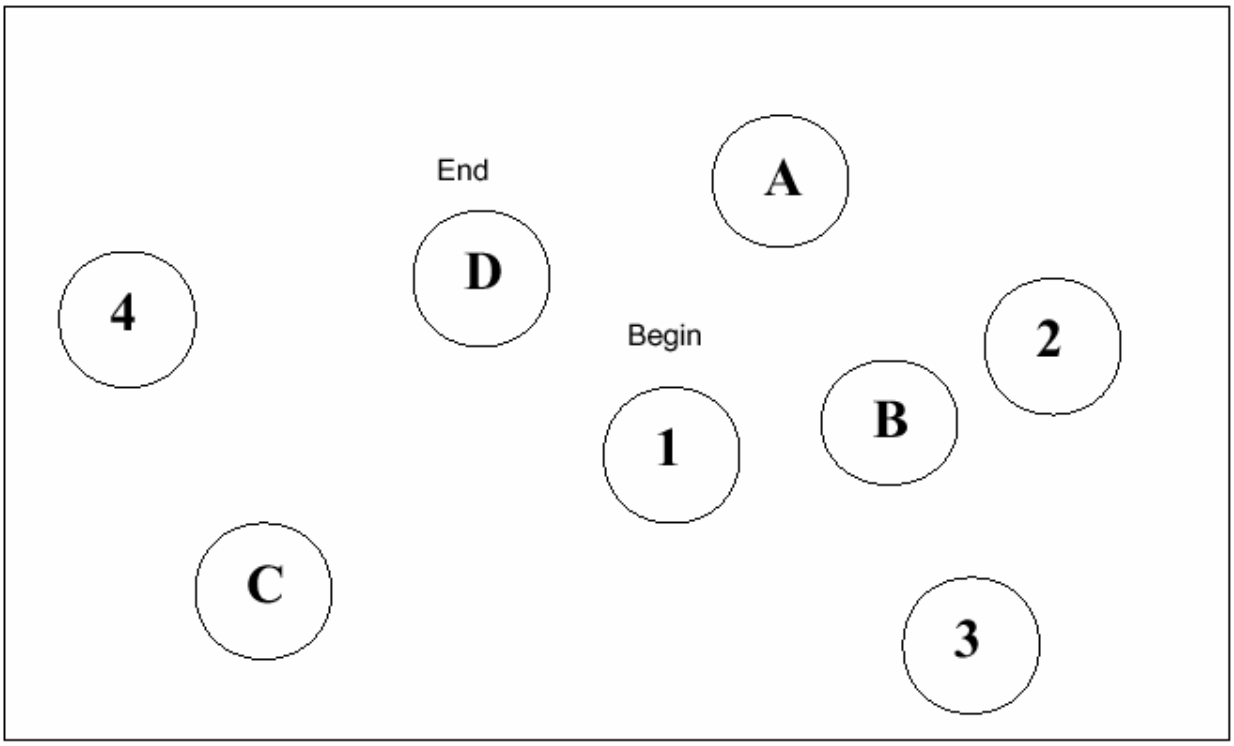
Trail Making Test Part A – *SAMPLE*



Trail Making Test Part B



Trail Making Test Part B – *SAMPLE*



Appendix F: Design Copy Test

Design A

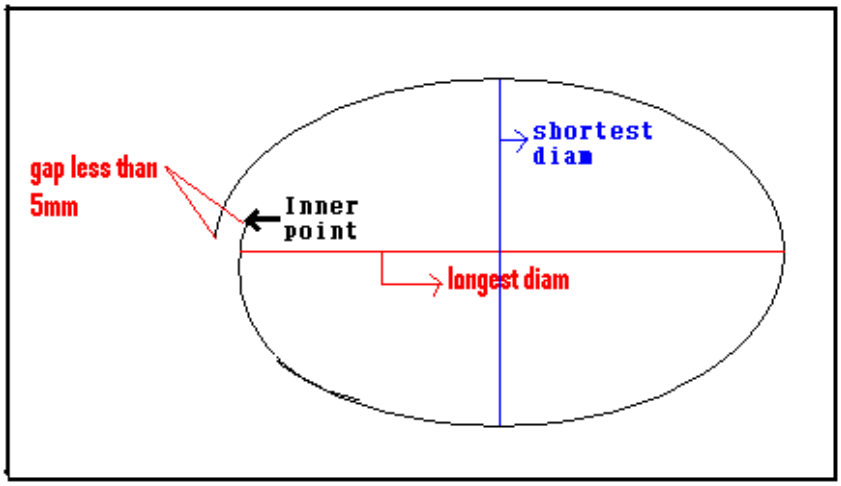


Figure A1. If the gap is less than 5mm, then use the inner point when measuring a diameter.

The ratio of diameters needs to be ≤ 1.5.

Design B

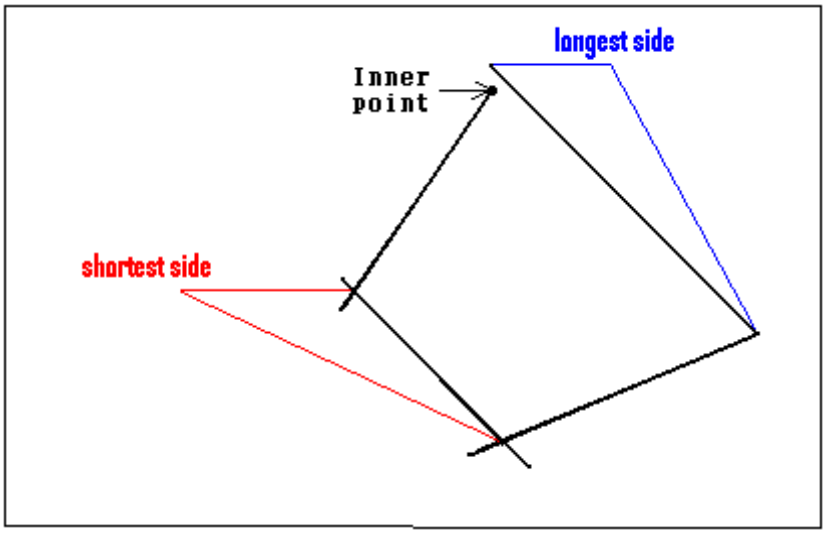


Figure B1. If the gap is less than 5mm, then use the inner point when measuring a diameter.

The ratio of diameters needs to be ≤ 1.5.

Design C

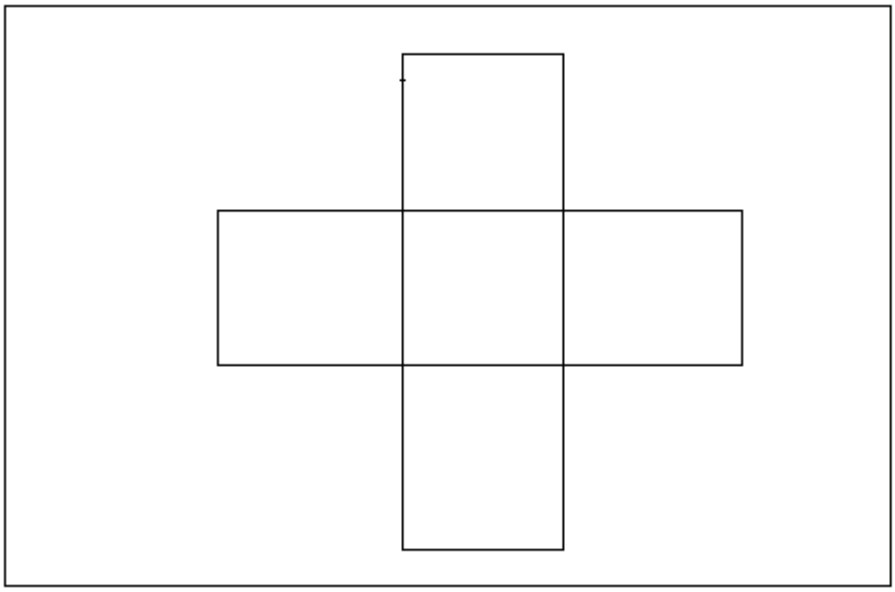


Figure C1. Figures are four-sided and overlap does resemble original.

Criteria a) Figs are 4-sides: **1 point**

Criteria b) Overlap resembles original: **1 point**

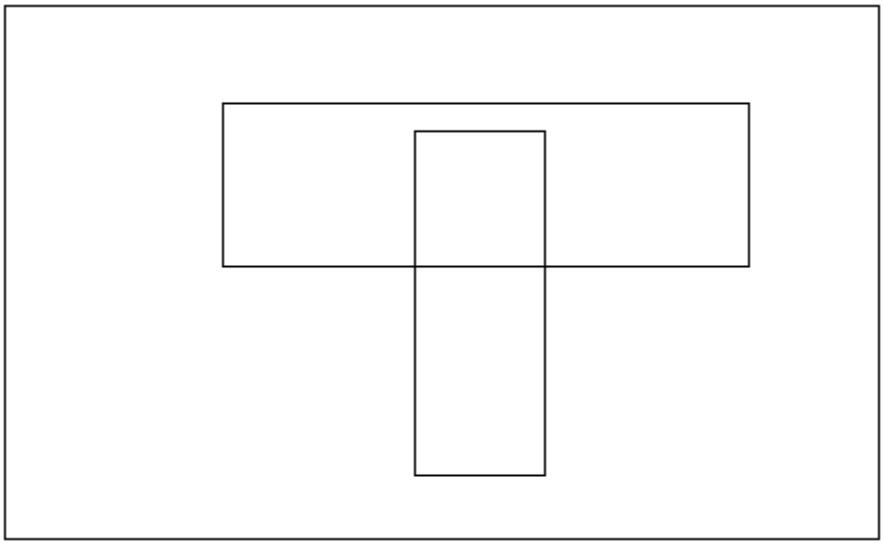


Figure C2. Figures are four-sided, but overlap does not resemble original.

Criteria a) Figs are 4-sides: **1 point**

Criteria b) Overlap resembles original: **0 point**

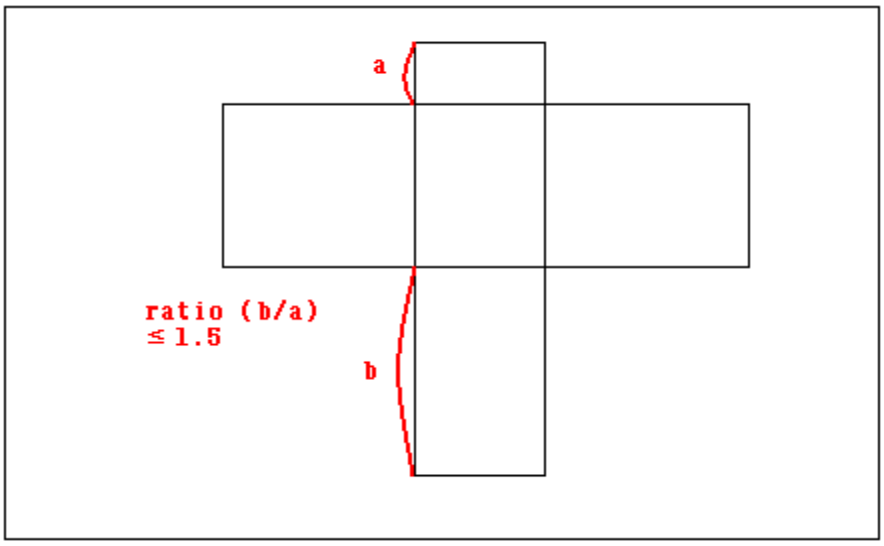


Figure C3. The ratio of non-overlapped sides needs to be ≤ 1.5.

Note. THINK clarification demonstrates how non-overlapped sides of approximate = length are determined.

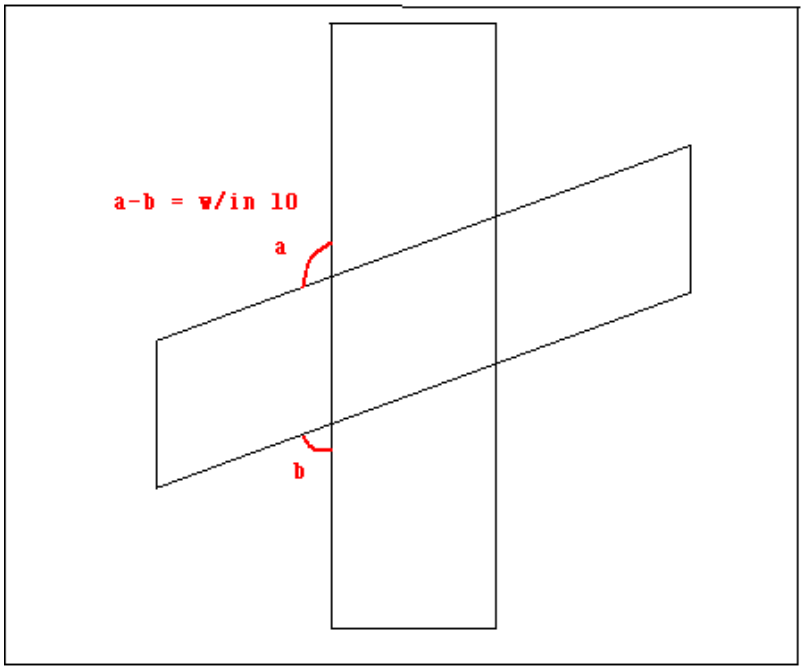


Figure C4. Two rectangles meet at right angles (a-b ≤ 10°).

Note. THINK clarification demonstrates the degree of angles deviated from right angels when two rectangles meet.

Design D

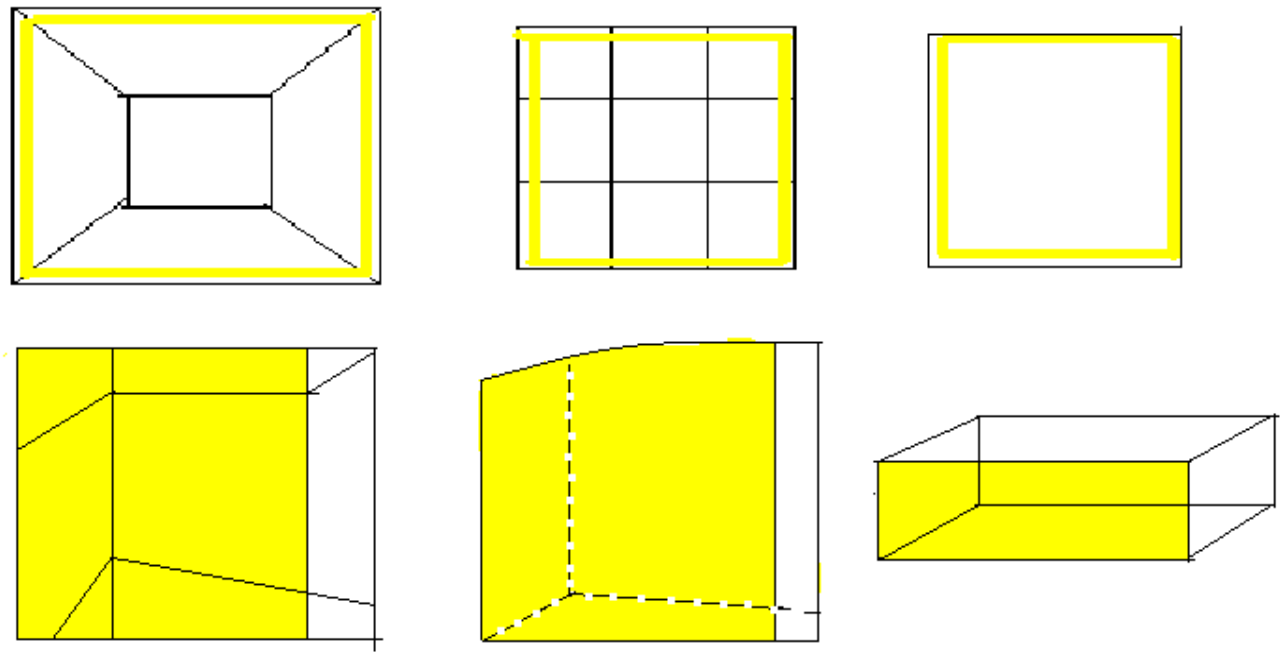
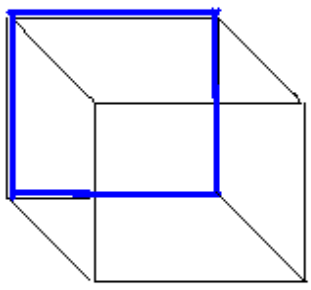
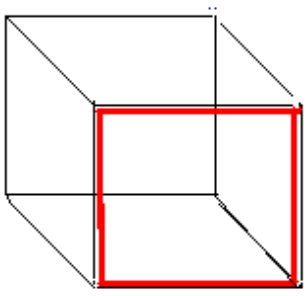


Figure D1. Examples of frontal face correctly oriented with base line even with horizontal plane.



Frontal face on Left side



Frontal face on Right side

Figure D2. Examples of frontal face correctly oriented on either Lt side or Rt side

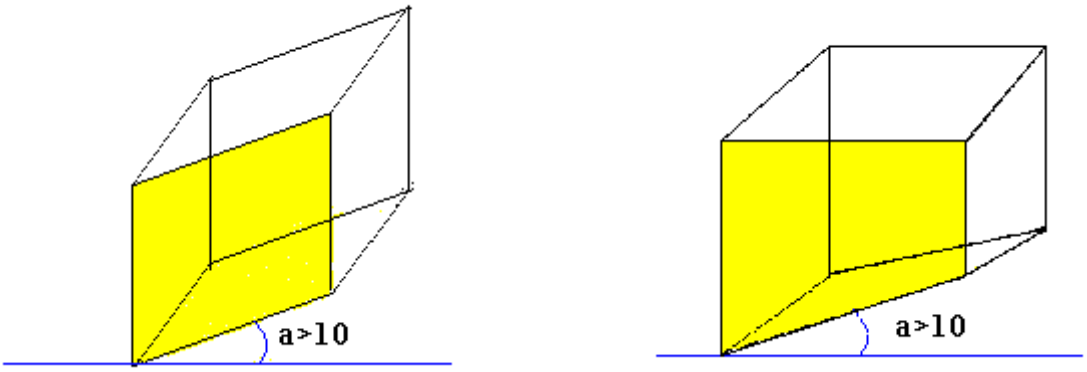
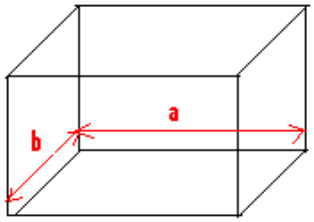
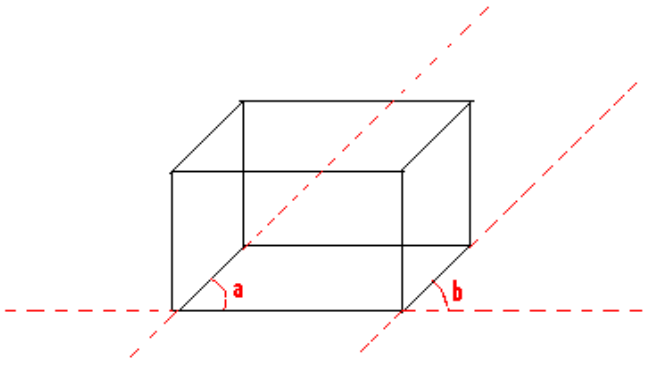


Figure D3. Examples of frontal face not correctly oriented: bottom line deviated > 10°



1.5 ≤ (a / b) ≤ 2.5

Figure D4. Internal lines must be present

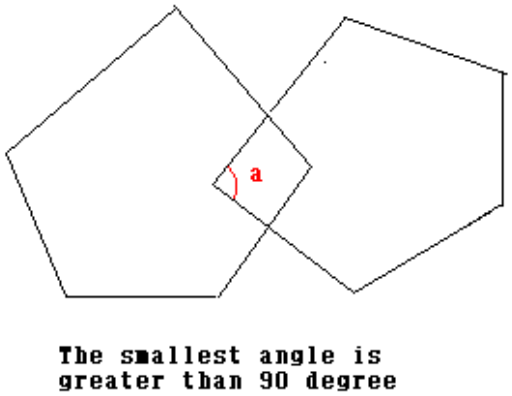


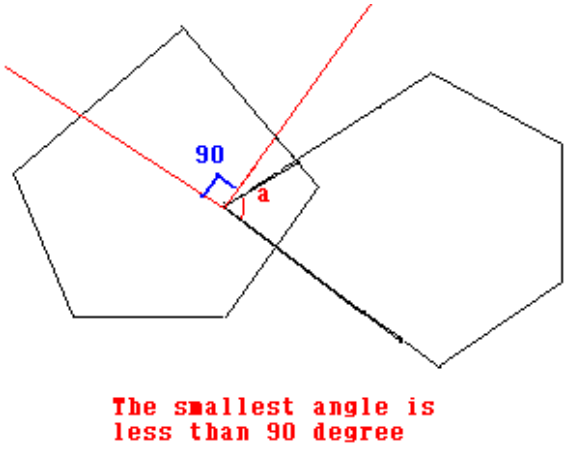
a – b ≤ 10°

Figure D5. Parallel within 10°

with the ratio of 1.5-2.5

Design E





Criteria a) two 5-sided figures (all angles > 90): **1 point**

Criteria b) Overlap: **1 point**

Criteria c) Intersection: 4-sided figure: **1 point**

Criteria a) two 5-sided figures (but not all angles > 90): **0 point**

Criteria b) Overlap: **1 point**

Criteria c) Intersection: 4-sided figure:**1 point**

Constructional Praxis Scoring

Item #1 Circle	
a) Closed circle (gap less than 5mm)	Incorrect……0 Correct…….1
b) Circular shape (longest diameter/shortest diameter ≤ 1.5) THINK clarification: 1. If gap less than 5mm, use inner point when measuring diameter (Design A)	Incorrect……0 Correct…….1
Item #2 Diamond	
a) Draw 4 sides (3 sides=0, 5 sides=0)	Incorrect……0 Correct…….1
b) Closes all 4 angles of figure (gap less than 5mm)	Incorrect……0 Correct…….1
c) Sides of approximate = length (longest side/shortest side ≤ 1.5) THINK clarification: 1. Point-to-point rule applies when measuring length, except for closed sides (Design B)	Incorrect……0 Correct…….1
Item #3 Rectangles	
a) Figures are 4 sides	Incorrect……0

	Correct…….1
b) Overlap resembles original Appendix C1: Meet the criteria Appendix C2: Variation that does not resemble original THINK clarification: 1. Non-overlapped sides of approximate = length (longest side/shortest side ≤ 1.5) (Appendix C3) 2. Two rectangles meet at right angles (w/in 10°) (Appendix C4)	Incorrect……0 Correct…….1

Item #4 Cube	
a) Figure is 3-dimensional (can exist, has volume)	Incorrect……0 Correct…….1
b) Frontal face correctly oriented THINK clarification: 1. Examples of variations of frontal face correctly oriented (Appendix D1) 2. Examples of variations of frontal face correctly oriented on either Rt or Lt side (Appendix D2)	Incorrect……0 Correct…….1

2. Examples of variations of frontal face not correctly oriented- deviation from the horizontal line > 10° (Appendix D3)	
c) Internal lines correctly drawn (all lines must be present) THINK clarification: 1. All internal lines must be present, with the ratio of base lines between 1.5 ~ 2.5 (Appendix D4)	Incorrect……0 Correct…….1
d) Opposite side parallel (w/in 10°, all lines must be present) THINK clarification: 1. Use the lines from the base when measuring angles (Appendix D5)	
Item #5 Pentagon	
a) Two regular 5-sided figures THINK clarification: 1. All angles > 90 (appendix E)	Incorrect……0 Correct…….1
b) Overlap	Incorrect……0 Correct…….1

c) Intersection is 4-sided figure	Incorrect……0 Correct……..1

Appendix G

Florida Cognitive Activities Scale

Activity	Never did this activity	Have not done this activity in the past year	Less than once per month	One to four times per month	Five or more times per month	Everyday
1. Playing chess, bridge, or knowledge games						
2. Playing board games of skill or chance						
3. Solving crossword puzzles, acrostics [a]						

Activity	Never did this activity	Have not done this activity in the past year	Less than once per month	One to four times per month	Five or more times per month	Everyday
4. Watching TV/listening to radio [b]						
5. Listening to music [b]						
6. Gardening						
7. Reading newspaper [b]						
8. Reading books/stories [a,b] 9. Writing letters [a]						

Activity	Never did this activity	Have not done this activity in the past year	Less than once per month	One to four times per month	Five or more times per month	Everyday
10. Talking on the phone/visiting [b]						
11. Doing original art/craft work [a]						
12. Doing art or craft kits/patterns [a]						
13. Making complex home repairs						

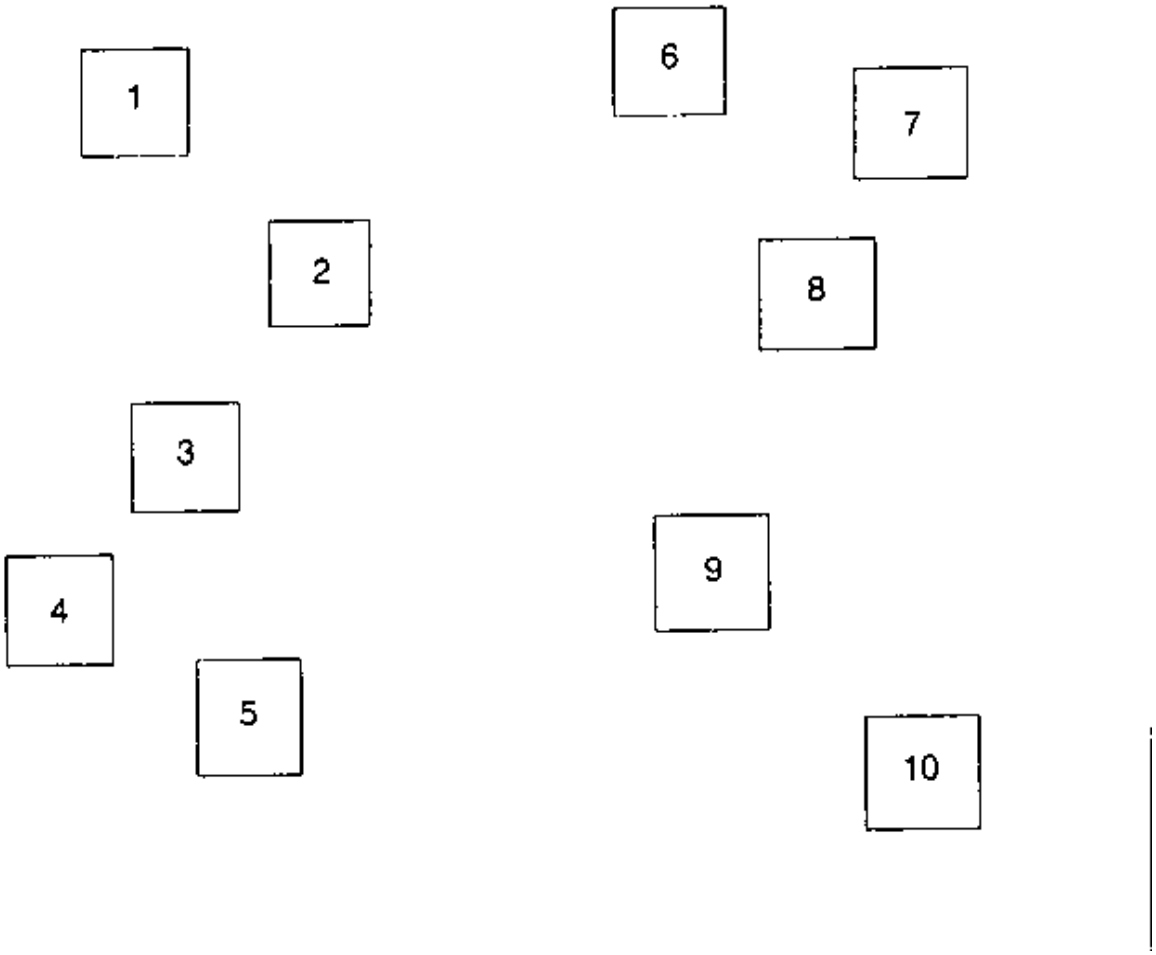
Activity	Never did this activity	Have not done this activity in the past year	Less than once per month	One to four times per month	Five or more times per month	Everyday
14. Making simple home repairs						
15. Preparing meals from new recipes [a]						
16. Cooking familiar recipes [a, b]						
17. Leading discussions						
18. Taking a course						

Activity	Never did this activity	Have not done this activity in the past year	Less than once per month	One to four times per month	Five or more times per month	Everyday
19. Managing of investments						
20. Doing routine financial work						
21. Walking/driving in unfamiliar places [a]						
22. Walking/driving in familiar places [b]						

Activity	Never did this activity	Have not done this activity in the past year	Less than once per month	One to four times per month	Five or more times per month	Everyday
23. Going to social clubs						
24. Attending church/religious activities [a]						
25. Shopping [b]						

Appendix H

Corsi Block-tapping task



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