Comparing Alzheimer's Disease and Vascular Dementia Profiles on Neuropsychological Tests among Japanese Elders

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Dedications

I would like to dedicate my long journey in graduate school to my parents, Yoshinori and Shoko Sakamoto. They have always encouraged, inspired, and believed in me. I hope my mother is watching my growth and smiling from TENGOKU.

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ABSTRACT

Comparing Alzheimer's Disease and Vascular Dementia Profiles on Neuropsychological Tests among Japanese Elders
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Dementia is a devastatingly serious problem in industrialized countries, such as Japan and the United States. The most prominent dementia subtypes: Alzheimer's disease (AD) and vascular dementia (VaD) show a different pattern in these two countries. Most research studies on cognitive aspects of dementia have been conducted in western countries, but not in Japan, because of its short history of neuropsychology. To date, there has been only one Japanese study, and a criticism of this study is that it used tests that were insufficient and not culturally appropriate. It is necessary to explore what neuropsychological tests are sensitive and appropriate for a Japanese population in order to lead to more accurate diagnosis treatment strategies.

The present study aimed to identify valid neuropsychological tests for Japanese elders and to examine test profiles of AD and VaD in comparison to what is known in western neuropsychology. Five cognitive domains: executive control, information processing speed, visuospatial/construction, language, and learning and memory were evaluated. Seventy Japanese elders (30 healthy controls, 20 AD patients, and 20 VaD patients) participated in this study.

The present study indicated the usability of verbal learning and spatial memory tests, visuospatial/constructional tests, and a semantic fluency test for differentiating Japanese AD and VaD. These results suggest that Japanese AD patients showed a similar neuropsychological profile as that found in western studies (i.e. impairment in memory,

visuospatial, and semantic knowledge). Japanese VaD patients, however, demonstrated less severity in executive control and motor slowness as compared to American VaD patients. It is possible that Japanese VaD patients have fewer white matter changes in the frontal lobe, and/or cultural factors, especially intensive training in pictorial written language (Kanji), might impact VaD patients' cognition.

The present study was the first study to evaluate the usability of a culturally appropriate neuropsychological test battery for distinguishing between Japanese AD and VaD. A new Japanese Verbal Learning test, the PVLT-J was developed particularly for the study. This study has immediate clinical utility for use in dementia diagnosis in Japan, and it is hoped that it will spur more research in comparative brain-behavior processing across cultures.

CHAPTER 1. INTRODUCTION

Dementia has become a serious problem in industrialized countries, such as the United States and Japan, where people's life expectancies have increased (Fillenbaum et al., 2005; Gao, Hendrie, Hall, & Hui, 1998). The number of people 65 and older between 1990 and 2020 is suggested to grow 1.3 times in the United States and 2.2 times in Japan (United Nations, 2003). Researchers in these countries along with other industrialized countries have been actively studying the mechanisms of dementia. Through advancing technology and researchers' efforts, new information regarding different types of dementia has emerged.

Alzheimer's disease (AD) and vascular dementia (VaD) are the two most prominent dementia subtypes in both the United States and Japan (Welsh-Bohmer & Warren, 2006). Research on AD began in the early 20th century when Alois Alzheimer reported that his patient Auguste D., who had shown memory impairments, had neurofibrillary tangles and amyloid plaques in her brain at autopsy. Since then, the pathology and neuropsychology of AD has been vigorously studied and new important information has been revealed (Welsh-Bohmer & Warren, 2006).

On the other hand, VaD has only been recognized more recently. Initial conceptualization of VaD entailed only multi-infarct dementia (Libon, Price, Davis-Garrett, & Giovannetti, 2004). However, since the mid 1980's to the early 1990's, more researchers began to study small vessel vascular disease and its relationship with behavioral disturbances in greater depth (Filley, 2001; Lamar, Price, Davis, Kaplan, & Libon, 2002; Stuss & Cummings, 1990). With better understanding of mechanisms of VaD, clinicians and researchers started engaging in differentiating AD and VaD in terms of brain-behaviors since accurate diagnosis and early treatment may lead to better prognosis. However, the majority of studies examining how AD and VaD patients perform differently on neuropsychological tests are conducted in western countries. Those western studies report that memory and language are prominent impairments for AD and frontal and executive control abilities and information processing speed are the primary deficits for VaD (Looi & Sachdev, 1999; Oosterman & Scherder, 2006). In spite of the fact that dementia is a serious problem for Japanese elders, there is only one study which compares neuropsychological profiles between AD and VaD among Japanese elders. It is furthermore critical to better understand how AD and VaD affect Japanese elders' cognition and behaviors.

Because of a short history of neuropsychology, Japanese clinicians often use cognitive assessments developed in western countries by translating them into Japanese. However, it is well documented that cultural differences strongly influence the performance on testing. In addition to other cultural differences, Japan has a unique writing system, using a pictorial written language called Kanji. Studies have demonstrated that intensive and lifelong Kanji education enhances Japanese individuals' visuospatial abilities (Bond, 1980; Gitterman & Sies, 1992; Flaherty & Connolly, 1995; Sakamoto, 2006). It is highly possible that Kanji training influences other cognitive domains such as memory, language, information processing speed, and executive control abilities. However, it is unclear how Japanese individuals, especially Japanese elders, perform on neuropsychological tests examining those cognitive domains. If Japanese and American people differ in their neuropsychological functioning, then AD and VaD may differentially affect brain-behavior relations across these cultures. In order to examine the similarities and differences in neuropsychological profiles of Japanese AD and VaD patients, it is crucial to carefully select culturally appropriate and sensitive assessments for Japanese elders.

This study aimed to 1) identify appropriate neuropsychological tests to differentiate Japanese AD and VaD and 2) examine how Japanese AD and VaD patients perform on those tests. In this section, six important components will be discussed:

a) Different neuropsychological profiles between AD and VaD in western cultures

b) The importance of differentiating AD and VaD in Japan

c) The impact of cultural differences between Japan and the U.S. on AD and VaD

d) The validity of western neuropsychological assessments to Japanese elders

e) Possible cultural differences in cognition in AD vs. VaD

f) Identifying appropriate tests for Japanese profiles of AD vs. VaD.

1.1.1. Different Neuropsychological Profiles between AD and VaD in Western Cultures

Studies that are conducted in western countries report that there are measurable group differences in neuropsychological profiles between AD and VaD (Cummings, Miller, Hill, & Neshkes, 1987; Erkinjuntti & Rockwood, 2001; Jorm, et al., 1993; McPherson & Cummings, 1996; Sachdev & Looi, 2003). Generally, AD patients perform poorly on memory and language/semantic knowledge tasks whereas VaD patients perform worse on frontal and executive functions, and information processing speed (Looi & Sachdev, 1999; Oosterman & Scherder, 2006). Each important cognitive domain will be reviewed to better understand the unique patterns of performance of AD and VaD as they have been examined in western cultures.

Memory

Memory is the predominant impairment in AD (Reed et al., 2007). Studies report that VaD patients outperform AD patients (Looi & Sachdev, 1999; Mendez & Asla-Mendez, 1991; Padovani et al., 1995). VaD patients generally perform better on short-delay recall, long-delayed recall, and recognition (Libon et al., 1997; Looi & Sachdev, 1999; Padovani, et al., 1995; Villardita, 1993). VaD also presents memory deficits; however, the characteristics of the deficits observed in AD and VaD are different in terms of quality and quantity. While patients with AD show encoding problems such that they do not benefit from the cued recall or delayed recognition trial for both verbal (i.e. California Verbal Learning Test and Philadelphia repeatable Verbal Learning Test) and non-verbal tasks (i.e. Rey-Osterrieth Complex Figure Test), patients with VaD usually did not show that encoding problem (Reed et al., 2007; Libon et al., 1997; Looi & Sachdev, 1999, Padovani et al., 1995). Rather, VaD patients have difficulty retrieving the information with evidence that they display benefit from cued recall or recognition test conditions (Libon, Price, Davis-Garrett, & Giovannetti, 2004; Looi & Sachdev, 1999). Patients with AD also have more false positive and intrusion errors than do patients with VaD (Lafosse, Reed, Mungas, Sterling, Washbeh, & Jagust, 1997).

Language

Looi and Sachdev's meta-analysis revealed that half of the studies found no performance differences on language tests between AD and VaD (Looi & Sachdev, 1999). The studies, which successfully differentiated AD and VaD, found that AD patients outperformed VaD patients on the Letter Fluency Test (Padovani, Di Piero, Bragoni, Iacoboni, Gualdi, & Lenzi, 1995; Mendez, Charrier, & Perryman, 1997) and the Boston

Naming Test (BNT) (Barr, Benedict Tune, & Brandt, 1992; Cosentino et al., 2004; Villardita, 1993). However, it is controversial whether AD patients perform better than VaD patients on the BNT since it requires semantic knowledge. Lukatera et al. (1998) analyzed the errors that AD and VaD patients made on the BNT and found that patients with AD made more superordinate errors (e.g., "bird" for pelican) whereas patients with VaD produced more coordinate errors (e.g., "seagull" for pelican) (Lukatera, Malloy, Jenkins, & Cohen, 1998). It is reported that AD patients are more likely to perform better on the letter fluency and worse on the category test (e.g., Animal Naming test), whereas the opposite profile is found in VaD patients (Carew, Lamar, Cloud, Grossman, & Libon, 1997; Henry, Crawford & Phillips, 2004; Monsch et al., 1997). In their most recent study, Rascovsky and her colleagues suggested that the disparity between letter and semantic category fluency impairments might be an indication of differences in the relative contribution of frontal-lobe-mediated retrieval deficits and temporal-lobe-mediated semantic deficits by comparing AD and temporal frontal dementia with autopsy confirmation (Rascovsky, Salmon, Hansen, Thal, & Galasko, 2007).

Executive Function

Although frontal lobe pathology is common in both AD and VaD (Lavretsky, 2006), executive deficits are not considered AD's primary impairment (Knopman & Selnes, 2003). Many studies report that patients with VaD perform more poorly than patients with AD on the executive function tasks, such as the Clock Drawing Test, the Similarities subtest of the WAIS, and the Letter Fluency Test (Garrett et al., 2007; Lamar, Price, Davis, Kaplan, & Libon, 2002; Lamar, Swenson, Kaplan, & Libon, 2004; Looi & Sachdev, 1999). It is suggested that the degree of leukoariosis, a measure of the white matter alteration, is associated with the severity of the executive dysfunction (Lamar et al., 2007, 2008). VaD patients tend to make more perseveration errors on tests such as the Wisconsin Card Sorting Test and Graphical Sequence Test, than the AD patients (Garrett, Paul, Libon, & Cohen, 2004; Padovani et al., 1995; Starkstein et al., 1996). The severe perseveration errors may be associated with the deficits in establishing and maintaining mental sets (Lamar et al., 1997). VaD patients are resistant to redirection and feedback. More specifically, Lamar et al. (1997) reported that subcortical ischemic vascular dementia patients made more motor-related perseverations. In their study, patients with AD also demonstrated perseveration; however, it was related more to language and conceptualization. More recent study revealed that AD patients tended to show inhibitory control dysfunction associated with context-specific errors, which was considered higher level of executive function, whereas VaD patients made more perseveration and inhibitory control deficits related to non-context specific errors (Lamar et al., 2004). In other words, AD patients produce “close but not quite right answers” while VaD patients are unable to generate answers that are even in the right direction due to their inability to establish mental sets.

Working Memory

Working memory has aspects of executive control. It is often assessed by the Digit Span Backward Task, Trail Making Test, and Stroop Test (Looi & Sachdev, 1999; Oosterman & Scherder, 2005). Studies reported that patients with AD outperformed patients with VaD on the Continuous Performance Test, Trail Making Test, and Digit Span Backward Task (Villardika, 1993; Mendez, Charrier, & Perryman, 1997; Starkstein et al., 1996). Oosterman and Scherder (2006) conducted a meta-analysis to identify the performance differences between AD and VaD and found that patients with AD outperformed the patients with VaD on the Digit Span Backward subtest on the WAIS-III. Lamar and her colleagues (2007) more specifically analyzed the relationship between leukoariosis and the performance on the Digit Span Backward Task. Although high degrees of leukoariosis witnessed in VaD patients did not interfere with just recalling numbers in any order, it did interfere with manipulating and re-ordering numbers in exact order (Lamar et al., 2007). It is crucial not only to look at overall performance but also to analyze the types of errors.

Psychomotor/Information Processing Speed

It is agreed that patients with VaD usually have more psychomotor retardation and motor dysfunction compared to patients with AD (Lavretsky, 2006; Garrett, Paul, Libon, & Cohen, 2004). It is often observed that VaD patients performed more poorly on the Digit-Symbol (DS) subtest and Symbol-Copy (SC) test of the WAIS than AD patients (Oosterman & Scherder, 2007). Moreover, a study showed that while AD patients performed significantly better on the SC than the DS, VaD patients performed unchangingly on those tasks (Sakamoto et al., 2007). The performance over time suggested that AD output on DS over the four 30-second epochs was basically constant; however, VaD output in the DS was characterized by a negative slope, which indicated reduced output over the four 30-second epochs. The slope for AD patients in the SC test indicated increasing output over the four 30-second epochs whereas VaD performance on the SC test over the four 30-second epochs remained constant (Sakamoto et al., 2007). Additionally, there were trends for VaD patients to make more perseverations and graphomotor errors in both test conditions (Sakamoto et al., 2007). Slow information processing speed in VaD may be attributed to disruption of motor association pathway (Sachdev & Looi, 2003).

Visuospatial/Construction Abilities

Whether or not there are differences in performance of visuospatial construction between AD and VaD is controversial (Looi & Sachdev, 1999). Some studies found no differences (Gfeller & Rankin, 1991; Padovani et al., 1995) while others found better performance of AD over VaD on the Clock Drawing Test, Block Design subtest, and Object Assembly subtest (Cosentino, Jefferson, Marissa, Price, Davis-Garrett, Swenson, & Libon, 2004; Kartesz & Clydesdale, 1994; Lamar et al., 1997, Libon, Malamut, Swenson, Sands, & Cloud, 1996). Especially, error analysis procedures for the Clock Drawing Test are able to differentiate VaD from AD (Cosentino et al., 2004). AD patients usually improve their performance on copy condition from demand condition. On the other hand, VaD patients' performance did not improve because VaD patients tend to perseverate. Careful error analysis may allow clinicians to observe performance differences between AD and VaD.

In summary, many western studies suggest that memory, language/semantic knowledge, executive control abilities, and information processing abilities are the important cognitive domains to differentiate AD and VaD. AD patients generally perform more poorly on memory and language/semantic knowledge tasks whereas VaD patients perform worse on frontal and executive function and information processing speed. It is controversial whether visuospatial/construction tasks differentiate AD and VaD. Thus, the unique patterns of performance on neuropsychological tests may be related to the anatomical and neuropathological characters of AD and VaD.

1.1.2. Neuropathology of Alzheimer's Disease

AD is characterized by the extracellular amyloid plaques and intracellular neurofibrillary tangles (Price et al., 1991). There are now neuropathological hallmarks for definitive post-mortem diagnosis of AD (Kandimalla, Curran, Holasek, Gilles, Wengenack, Ramirez-Alvarado, & Poduslo, 2006). The amyloid plaques are primarily composed of viscous transmembranes protein called amyloid β (Aβ) which is thought to be neurotoxic (Kandimalla et al., 2006). The amyloid plaques are found in large numbers in the limbic and associative cortices of AD patients and vary widely in size (Eriksen & Janus, 2007). Neurofibrillary tangles are found within neurons and composed of various hyperphosphorylated forms of the microtubule associated protein tau. In AD, the neurofibrillary tangles affect large regions of brain including frontal, temporal, parietal, occipital associative cortices, the entorhinal cortex, hippocampus, parahippocampal gyrus and amygdale (Eriksen & Janus, 2007). The abnormal cross-linking of the proteins causes massive disturbances in microtubular arrays. This leads to the inability of supporting normal intracellular transport of proteins, and as a result, neuronal death (Welsh-Bohmer & Warren, 2006). It is suggested that the neurofibrillary tangles are observed in the entorhinal cortex in early stage of the disease, and then spread to the hippocampus while damaging the pathways from the hippocampus to the rest of the cortex (Braak & Braak, 1997; Hampstead, 2006). Considering the importance of medial temporal lobes including parahippocampal, perirhinal, and entorhinal cortices and the hippocampus for the formation of new memories (Squire & Zola-Morgan, 1991) as well as semantic knowledge (Saffran & Schwartz, 1994), it is understandable that impairments in memory and semantic knowledge are often witnessed in the early stage of AD and progressively worsen as the disease progresses.

1.1.3. Neuropathology of Vascular Dementia

Unlike AD, the neuropathology of VaD is more complex; therefore, the clinical presentations of VaD can be heterogeneous. However, Olsson, Brun, and Englund (1996) proposed that it is helpful to categorize underlying events of VaD into extra-cranial and intra-cranial disease by identifying fundamental pathological lesions.

Extra-cranial disease includes atherosclerosis, emboli, and thrombi (Libon, Price, Davis-Garrett, & Giovannetti, 2004). Atherosclerosis is caused by gradual buildup of fibroblasts and often affects both large and small vessels. Atherosclerotic process is highly linked to the increased risk of lacunar infarcts (Vinters et al., 2000). Emboli originate from either heart or lungs, travel through the bloodstream, and often block branches of one of the three major cerebral arteries (Libon, Price, Davis-Garrett, & Giovannetti, 2004). Thrombi are associated with endothelial cell damage of arteries (Capron, 1988), and eventually reach the brain (Libon, Price, Davis-Garrett, & Giovannetti, 2004).

Cerebrovascular disease that involves intra-cranial vessels is often associated with subcortical vascular pathology (Libon, Price, Davis-Garrett, & Giovannetti, 2004). It is suggested that the deep subcortical white matter vascularization may be vulnerable to injury caused by alterations or decrease in cerebral blood supply because of its anatomy (de Reuck, 1971; Libon, Price, Davis-Garrett, & Giovannetti, 2004). Also, the deep subcortical white matter may be easily compromised due to secondary effects of disease, particularly ischemia (Patoni & Garcia, 1997).

The damage caused by extra or intra-cranial disease leads to cognitive impairments and behavioral disturbances. In general, the severity and types of impairments depend on the location and the amount of damaged neurons. In spite of the heterogeneity of VaD neuropathology, common areas that are vulnerable to cardiovascular syndromes are found. For instance, a cerebral blood flow study demonstrated that cerebral hypoperfusion is primarily present in the frontal areas in VaD (Nagata et al., 2000). As discussed earlier, deep subcortical white matter is also vulnerable to cerebrovascular disease due to anatomical reasons. These more common pathologies may result in the prominent cognitive impairments of VaD such as executive dysfunction and psychomotor slowing.

1.1.4. Importance of Differentiating AD and VaD in Japan

Many studies have demonstrated that AD and VaD have unique clinical presentations; however, the majority of the studies were conducted in western cultures. There is only one Japanese study which tried to differentiate mild AD and mild VaD by assessing different cognitive domains (Tei et al., 1997). In the Japanese study, attention and mental processing speed, language, verbal memory, visual memory, visuo-construction ability, and executive control ability were assessed. Tei and his colleagues utilized the Symbol Digit Modality Test, Letter Pick-Out Test, Letter and Semantic Fluency Tests, Digit Span Forward Test, Rey Auditory-Verbal Learning Test, Ray-Osterrieth Complex Figure Test, and Wisconsin Card Sorting Test. They found that AD patients performed more poorly on visuospatial memory and VaD performed worse on executive control abilities (Tei et al., 1997). It is surprising that AD did not show inferior performance to VaD on verbal memory since memory impairment is a prominent problem universally observed from the early stage of disease (Graves et al., 1999). Memory impairment is also considered a first indication of AD in Japanese dementia cases (Hasegawa, 1983). There are two possible explanations for why AD and VaD performed similarly on verbal memory: either memory functions of Japanese AD and VaD patients are similar at the early stage of disease, or the assessment did not adequately differentiate the problem among Japanese elders.

Tei and his colleagues (1997) used the Rey Auditory-Verbal Learning Test (RAVLT) to assess verbal memory. As discussed earlier, studies conducted in western countries have reported that patients with AD show encoding problems whereas patients with VaD usually show retrieval problems (Reed et al., 2007; Libon et al., 1997; Looi & Sachdev, 1999, Padovani et al., 1995). In order to differentiate those two types of memory deficits, cued recall, delayed recall, and recognition trials are essential in verbal learning tests. Tei and his colleagues assessed immediate recall and delayed recall, but did not include the cued recall or recognition trials of the RAVLT. It is possible that Tei et al. might have failed to capture the Japanese mild AD patients' encoding deficits. It is therefore important to examine how Japanese AD and VaD patients perform on delayed recall, cued recall and recognition.

It is also quite possible that the study results are valid; that is, Japanese AD and VaD participants may not differ in verbal memory abilities. Tei et al. (1997) reported that both AD and VaD scored significantly lower than healthy controls on the trial 5 and

6 of the RAVLT. However, it is premature to conclude that AD and VaD in Japanese patients have similar memory profiles at the early stage of disease from one study. In fact, the Japanese VaD outperformed the Japanese AD on the delayed recall of spatial memory task. In order to determine whether Japanese AD and VaD in fact show different memory profiles from western AD and VaD, it is crucial to conduct a similar assessment of verbal memory, but with greater attention to the variables which have differentiated AD and VaD.

As with memory, it is unclear why Japanese AD and VaD showed no significant differences in language and information processing. Again, it could be due to inadequate assessment tools or, more straightforwardly, due to similar performance between Japanese AD and VaD. Tei's study was conducted 10 years ago and newer studies conducted in western countries have been proposing specific tests to assess specific cognitive domains that are important for differentiating AD and VaD. By using those assessment tools, we may be able to better understand whether AD and VaD impact Japanese elders' cognition in a different way than they do Americans'. Therefore, it is essential to carefully select adequate neuropsychological tests that may be able to differentiate Japanese AD and VaD and to investigate how these two groups perform similarly or differently on the tests.

There is another reason why it is crucial to explore the field of differentiating between Japanese AD and VaD in depth. The incidence rates of AD and VaD in the United States and Japan are reversed although AD and VaD are prominent subtypes of dementia in both countries (Welsh-Bohmer & Warren, 2006). For instance, it was reported that the ratio of AD and VaD was 1.7 in the western nations while the ratio was reversed in Japan (AD: VaD, 0.5) (Jorm, Korten, & Henderson, 1987; Tatemichi, Sacktor, & Mayeux, 1994). The differences in incidence rates could be due to biological susceptibility (Hallman et al., 1999) and/or lifestyle differences between two countries. They may alter the risks for different subtypes of dementia, AD and VaD (Graves, Rajaram, Bowen, McCormick, McCurry, & Larson, 1999; Larson, McCurry, Graves, Bowen, Rice, McCormick et al., 1998).

In the *Ni-Hon-Sea Study*, Japanese elderly men who were living in mainland Japan, Hawaii, and Washington State were compared (Larson et al., 1998). When the ratio of AD to VaD was compared in the three cultural groups, the ratios changed progressively from an Asian to a western pattern: 0.55 for Japan; 0.67 for Hawaii; and 2.0 for Washington. The shift across three genetically related but culturally diverse groups suggests a great influence of culture on the incidence rates of AD and VaD (Larson et al., 1998).

Another cross-cultural study which compared the Japanese population in Okinawa, Japan, and Brazil found that the Japanese elderly in Japan showed lower incidence rates of AD and VaD (Yamada et al., 2002). This study suggested that dietary differences, such as that the Japanese Brazilian eat more meat and less fish than the Japanese in Okinawa who consume more fish and less meat, created the different incidence rates since the two cultural groups have similar biological backgrounds. As a matter of fact, there are studies indicating the importance of dietary factors to reduce dementias (Mizushima, et al., 1997). Fish consumption has been inversely related to the incidence of dementia, especially AD (Kalmijn, Lauren, Ott, Wiiteman, Hofman, & Breteler, 1997). The n-3 PUFA in fish has anti-inflammatory properties (Blok, et al., 1996) and inflammation is now believed to be closely related with AD pathophysiology (McGeer & McGeer, 1995).

These epidemiological studies propose that cultural factors greatly influence the prevalence of AD and VaD. In other words, different lifestyles may increase or decrease the risk factors for AD and/or VaD. However, these studies do not provide information regarding how AD and VaD impact Japanese elders in terms of cognitive functions. It is still unknown how differently or similarly AD and VaD affect Japanese cognition as compared with American cognition. Since VaD is preventable and has effective treatment, it is important to differentiate VaD from AD in early stage of illness. Accurate diagnosis and early treatment are the crucial key factors to prevent the progression of the syndromes, which leads to reduction of the burdens to the associated families. In Japanese society, it is tradition and culture that family members nurse their loved ones who suffer from dementia at home instead of sending them to nursing homes. Thus, it is urgent to study further AD and VaD in Japanese culture.

1.2.1. Impact of Cultural Differences between Japan and the U.S.

It is well documented that cultural factors affect cognition (Amponsah, 1997; Amponsah & Krekling 2000; Feingold, 1994; Orsini, Schiappa & Grossi, 1981; Orsini, Simonetta & Marmorato, 2004; Silverman, Phillips & Silverman, 1996). How Japanese individuals perceive things, think, and solve problems may be different from Americans. Again, if how the brain works is different between Japanese and Americans, it is possible that AD and VaD affect Japanese brains differently from American brains. In order to examine how AD and VaD affect Japanese elders' brain-behaviors, we have to administer a variety of neuropsychological tests to Japanese elders and examine how they perform. However, the validity and reliability of the tests for the Japanese that were developed and standardized in western countries is greatly in question.

1.2.2. Validity of Western Neuropsychological Assessments to Japanese Elders

Development of psychological and neuropsychological assessments began in European countries in the early 20th century (Gardner, 1999). Binet and Simon are considered the developers of the first psychological assessment. Their goal was to develop a comprehensive battery of tests to distinguish children with mental retardation from those with behavioral problems. Binet and Simon's success motivated other psychologists such as David Wechsler, an American, and led to the development of other intelligence and cognition assessments including the Wechsler Adult Intelligence Scale (WAIS) (Chan, Shum, & Cheung, 2003).

The development of psychological assessments in Asia started much later because both academic and professional psychology in most Asian countries did not establish themselves until the mid-20th century. Moreover, the psychological literature published in western culture was not available to psychologists in Asian countries until recently (Chan, Shum, & Cheung, 2003). When it became available, Asian psychologists and scientists started using the assessments that were developed in the west, instead of creating their own assessments, because many assessments had already established their validity and reliability in those western countries at that time (Chan, Shum, & Cheung, 2003). Japan is no exception. Many western neuropsychological tests were adopted and directly translated into Japanese. However, the issues regarding cross-cultural validity of the assessments as well as the norms have arisen since not only language differences but also other environmental differences impact the performance on testing.

It is especially important to take into account cultural factors when discussing brain diseases, such as AD and VaD. Some research studies have suggested the brain works differently in Japanese and Americans (Aldila, 2003; Nisbett & Masuda, 2006; Sakamoto, 2006). Living in a homogeneous and traditional Japanese culture for seven or eight decades may produce different patterns of cognitive functions. Differences in thinking process, perception, and strategies used in daily life may create different ways of brain functions between Japanese and Americans. If the two cultural groups use their brains differently throughout their lives, it would not be surprising that AD and VaD affect Japanese and Americans' cognition differently. It is important to discuss more specifically what cognitive domains may show unique cultural differences in AD vs. VaD.

1.2.3. Possible Cultural Differences in Cognition in AD vs. VaD

Japanese and Americans may have different patterns of brain functions (Aldila, 2003; Nisbett & Masuda, 2006; Sakamoto, 2006). There is no neuroimaging study evaluating whether Japanese elders and Americans elders use their brains differently on the same tasks; therefore, it is difficult to predict how differently or similarly elders in the two cultural groups would perform in specific cognitive domains. However, behavioral studies in psychology and anthropology are useful resources to explore certain cognitive domains that possibly show cultural differences in cognition in AD and VaD. The important cognitive domains that are crucial when discussing AD and VaD in Japanese culture will be discussed. These are spatial abilities, executive functioning, information processing, memory, and language.

Visuospatial/Construction Abilities

One of the largest cultural differences between the U.S. and Japan are the writing and reading systems. Japanese written language relies on three types of forms: Hiragana, Katakana, and Kanji. Both Hiragana and Katakana are phonological letters, like those found in the Roman alphabet; however Kanji utilizes pictorial characters. Approximately 1,050 complex pictorial characters are commonly used in Japanese daily life. The three Japanese forms are taught in school, but Kanji is the most difficult form to learn and as a result is taught in school up to high school or even in college. Moreover, families encourage their children to perfect the written execution and visual mastery of these characters. Hatano (1990) suggests this process is a "cultural imposition." The vigorous visual training, which includes the visual processing skills, formation of images, and attention to detail involved in learning these complex symbolic characters throughout life, may facilitate accurate processing of pictorial information (Bond, 1980; Gitterman & Sies, 1992). Interestingly, a longitudinal cross-cultural study found that Japanese Americans who had more traditional Japanese lifestyles and were more exposed to the Japanese language (Kanji) as children and adults had a lower risk of experiencing cognitive decline over a 2-year follow-up period (Graves et al., 1999). This study suggests that living in a traditional Japanese culture, especially being exposed to Kanji education, may reduce risk factors for dementia, especially AD (Graves et al, 1999).

Also, the Japanese have a unique history in reading style. Before World War II, Japanese words used to be read from right to left when they were written horizontally.

Because Japan was influenced by western countries such as America and Britain, after World War II, the reading direction was changed from left to right. However, when Japanese is written vertically, the lines start from right and continue to the left. This mixed way of writing and reading from both right to left and left to right may influence both hemispheres of the visual fields (Fox, 1993). Because the majority of Japanese at risk for dementia were born before World War II when the written language was influenced by western countries, those Japanese elders may have unique ways to approach spatial performance tasks. How Japanese elders perceive and process objects may be different from American elders.

Grön and colleagues found different neural activation on the same visuospatial tasks between German and Chinese (Grön et al., 2003). Although Japanese individuals were not assessed in the study, Chinese use very similar writing and reading systems to the Japanese. Kanji is actually a Chinese written language that was conveyed from China and integrated in Japanese culture more than a thousand years ago. In Grön's study, Chinese and German participants were asked to solve the same spatial tasks while their brain neural activation was measured by fMRI. When the participants were learning new information, the dorsal stream (bilateral frontal and parietal cortex networks), which is also known as the "where" system, was actively working in the Chinese group. On the other hand, the ventral stream (fusiform gyrus and hippocampal complex network), which is known as the "what" system, was activated in the German group. Thus, the two cultures showed differences both in their behavioral strategies and in neural network activation (Grön et al., 2003). Japanese might also use the "where stream" rather than the "what stream" in performing spatial tasks.

A recent research study showed that young native Japanese individuals performed better on spatial performance tasks than Japanese Americans and European Americans due to mainly environmental differences since the native Japanese and Japanese Americans are genetically very similar (Sakamoto, 2006). Furthermore, when the strategy on the Rey-Osterrieth Complex Figure Test (ROCFT) was analyzed and compared between the three cultural groups, the usual sex difference in western populations showing men's preference for a more "holistic" strategy was not found in the native Japanese group (Sakamoto, 2006). In other words, both Japanese men and women used a very similar holistic approach to copy the complex figure. The longstanding vigorous Kanji training may have led Japanese women to perform in the same manner as Japanese men on the strategy although the ROCFT is considered as a male favoring task (Carole et al., 2004; Feingold, 1994; Silverman & Phillips, 1996).

Thus, Japanese cultural factors, and possibly the pictorial written language, may strengthen Japanese individuals' visuospatial abilities. Moreover, Japanese people seem to use holistic strategies for visuospatial tasks. Although many western studies failed to show differences between AD and VaD by using visuospatial tasks (Gfeller & Rankin, 1991; Loring, Meador, Mahurin, & Largen 1986; Villardita, 1993), because the Japanese study demonstrated superior performance of VaD patients on a visuospatial memory test (Tei et al., 1997), it is highly possible that AD and VaD affect Japanese elders differently from American elders. Since the underpinnings of how the brain works seems to differ between Japanese and Americans, examining spatial abilities may provide crucial information when differentiating AD and VaD among Japanese individuals.

Executive Functioning

As discussed earlier, the thinking processes and strategies that the Japanese use may be different from the Americans'. It is more likely that the Japanese solve high functioning problems by using more visual strategies whereas the Americans use more verbal strategies. Anthropological and cross-cultural studies reported that when causal attribution and prediction were assessed, western people tended to explain events by referencing to the properties of the object while Asians tended to explain the same events with reference to interactions between the object and the field (Choi & Nisbett, 1998; Choi, Nisbett, & Norenzayan, 1999; Morris & Peng, 1994; Nisbett & Masuda, 2006). For instance, when participants were shown cartoon displays of an individual fish moving in relation to a group of fish in various ways, Asian participants were more likely to see the behavior of the individual fish as a product of other fish: external factors. American participants tended to see the behavior more as being produced by factors internal to the individual fish (Morris & Peng, 1994). Different approaches to complex problem solving tasks may result in different neuropsychological profiles between AD and VaD in Japanese elders as compared to American elders. Nevertheless, the Japanese study demonstrated that VaD patients were significantly more dysexecutive than AD patients using the Wisconsin Card Sorting Test (Tei et al., 1997). The Japanese VaD patients were unable to find correct categories by learning from their mistakes because of the perseveration errors. The result is consistent with western studies, which also showed AD patients' impairments in executive functioning. Even though the thinking process and strategies are different between Japanese and Americans, the VaD neuropathology may impact individuals in those cultural groups in similar ways. Since there is only one

Japanese study, it is important to examine whether executive functioning impairments are prominent VaD deficits for both Japanese and American cultures.

Information Processing Speed

It is unclear how Japanese AD and VaD patients perform on tasks of information processing. Since Japanese are used to reading and writing symbol-like written language, Kanji, it is possible that minimal impairment in information processing in Japanese VaD group may be observed. The culture of reading and writing from different directions may also advantage Japanese elders' different information processing skills. In fact, the Japanese study did not differentiate between AD and VaD on the information processing tasks (Tei et al., 1997). In order to assess if the information processing abilities are less impaired in the Japanese VaD group, it is important to examine this cognitive domain.

Language

Japanese and English are two totally different languages in terms of grammar, pronunciation, and again, written systems. It would not be surprising if Japanese and American elders use different strategies and approaches to language tasks. Furthermore, the Japanese and Americans may show different brain activations when they speak their own language. Among different types of neuropsychological tests, verbal fluency and semantic fluency tasks may show unique neuropsychological profiles of Japanese AD and VaD because it is possible that Japanese individuals are having photographical images or Kanji characters when they are generating words. A Japanese neuroimaging study on AD showed a significant relationship between letter fluency tasks and only left prefrontal dysfunction whereas category fluency was more related to left temporal and prefrontal dysfunction (Kitabayashi et al., 2001). This brain activation is consistent with findings in western studies. On the other hand, it is believed that phonological letters (i.e. Hiragana, Katakana, and Roman letters) are interpreted at Brodmann's area 39 while Kanji is interpreted at Brodmann's area 37 (Uemura, 2006). Neural activations in different parts of the brain may result in different performances between AD and VaD groups on language tasks.

In terms of sex differences, it is thought that females generally perform better than males on verbal fluency tasks in western cultures (Weiss, Ragland, Brensinger, Bilker, Deisenhammer, & Delazer, 2006). However, a recent study reported that Malaysian elders did not show sex differences on verbal fluency task (Mathuranath, George, Alexander, Sarma, & Sarma, 2003). It is highly possible that Japanese elders also show no sex differences on verbal fluency tests. It is important to examine whether or not there are sex differences in verbal abilities among Japanese elders.

Memory

Memory functioning is composed of verbal memory and non-verbal memory. For verbal learning tasks such as the California Verbal Learning Test (CVLT) (Delis, Kramer, Kaplan, & Ober, 1987), there are several strategies. Some people may categorize the list of words based on families or categories while others may remember the list of words in the order they were given in. Categorical strategies are found in both Japanese and American cultures; however, how items are categorized seems different (Nisbett & Masuda, 2006). Asians have been found to classify items and events on the basis of relationships and family similarity whereas Americans tend to categorize on the basis of ruled-based category membership. For instance, when a chicken, cow, and grass were presented to American and Asian children, American children were more likely to choose the chicken and cow as they are both animals. On the other hand, Asian children tended to select the cow and grass as objects that could go together because "a cow eats grass." (Chui 1972; Nisbett & Masuda, 2006). Specific ways of categorization may not influence the accuracy of immediate recall as compared to no use of any categorical strategies at all; however, it is possible that the different categorical strategies may impact memory in long term. Furthermore, no Japanese studies reported how AD and VaD patients would benefit from cued recall and recognition; therefore, it is important to assess different types of verbal memory functions such as the ability to encode or retrieve newly learned information.

Assessing visuospatial memory is not as beneficial as testing verbal memory to differentiate AD and VaD in western cultures (Looi & Sachdev, 1999). However, visuospatial memory could provide unique information about AD and VaD among Japanese elders since visuospatial abilities are strengths of Japanese individuals. In fact, the Japanese study was able to differentiate between AD and VaD on a visuospatial memory test (Tei et al., 1997). The Japanese AD patients performed worse on the delayed recall of the ROCFT than the VaD patients. Perhaps, AD may more greatly affect Japanese elders than American elders. Japanese are visually and spatially oriented. Once they begin to suffer from AD, their visuospatial abilities to remember structures, shapes, locations, and details may become impaired at early stage of disease. The Japanese individuals' visuospatial strategies may no longer be useful or applicable for spatial memory.

Flaherty and Connolly (1995) found that Japanese individuals outperformed American individuals on spatial location memory tests. They also qualitatively reported that the Americans used more verbal strategies whereas the Japanese used more non-verbal and holistic approaches. AD neuropathology may damage the Japanese individuals' spatial strategies more severely than the American individuals' verbal strategies to remember the locations of items. Thus, assessing both verbal and non-verbal memory appears helpful to differentiate AD and VaD in Japanese culture.

In summary, it is crucial to assess whether those cognitive domains that differentiate AD and VaD in the west are also prominent for Japanese AD patients and VaD patients. Additionally, the only Japanese study has shown that the Japanese AD patients perform significantly poorly on a visuospatial memory test, ROCFT, although it is debatable for western researchers if the spatial memory abilities are significantly worse in AD than VaD (Looi & Sachdev, 1999; Tei et al., 1997). As the Japanese study suggests, it is crucial to replicate the study and assess how Japanese AD and VaD patients would perform on various neuropsychological tests, including visuospatial memory tasks. However, new research should select more sensitive neuropsychological assessments tools for cultural differences in dementia. This leads to the question of; what specific tests should be used in study differentiating Japanese AD and VaD?

1.3. Choosing Appropriate Tests for Japanese Profiles of AD vs. VaD

As mentioned earlier, there is only one study that has extensively examined performance differences between Japanese AD and VaD (Tei et al., 1997). It demonstrated significant differences in executive control and delayed spatial-visual memory. Many western studies have also shown significantly impaired performance in VaD as compared with AD on executive control, which is consistent with the Japanese study. However, other important cognitive domains that generally show significant performance differences between AD and VaD in western studies, such as verbal memory, language/semantic knowledge, and information processing speed did not show strong indication of AD or VaD neuropsychological profiles in the Japanese study. There may be in fact no differences between Japanese AD and VaD, or the neuropsychological assessments that Tei and his colleagues used might not be appropriate for the Japanese elderly. On the other hand, the Japanese study uniquely demonstrated that Japanese AD scored significantly lower than the VaD on the visuospatial memory test. As we discussed in the previous section, Japan has a distinctive culture including writing and reading systems, and they are believed to greatly influence Japanese cognition. Thus, specific assessments that may be able to differentiate Japanese AD and VaD in each cognitive domain should be carefully selected.

Visuospatial/Construction Tests

Since Japan has cultural factors that strengthen visuospatial construction abilities, such as lifelong Kanji experience, it is possible that VaD and AD may affect more or less the visuospatial abilities of the Japanese. In the Japanese study, only the Rey-Osterrieth Complex Figure Test (ROCFT) was used to assess visuospatial construction abilities (Tei et al., 1997). In order to more precisely examine what areas of spatial abilities may be affected by the brain diseases, several other spatial tests should be also administered and explored.

The Clock Drawing Test has been already used in Japanese society to detect dementia. Japanese clinicians do not use a specific error analysis, such as one that has been used for differentiation between AD and VaD in the U.S. (Barr, Benedict, Tune, &

Brandt, 1992; Libon et al., 1997). The US error scoring system appears valid and useful to assess Japanese elders' visuospatial abilities as well. The clock face, with numerical numbers, and arms are universal between the U.S. and Japan. Only one scoring item regarding counterclockwise drawing of numbers should be carefully observed. Japanese elders have a unique experience to read and write from right to left as well as left to right; therefore, it may be more acceptable for Japanese elders to draw numbers in a counterclockwise manner. The performance of healthy controls will be able to provide important information about drawing manner in Japanese elders.

The ROCFT has been widely used in Japan although no norms have been developed. The Japanese study failed to show different performances on the copy condition between AD and VaD; however, there is still the possibility that persons with VaD perform worse on the copy due to perseveration. In addition to the accuracy of the copy, and immediate and delayed recall, strategy on the copy should be also measured (Levy-Benett, 1984). The strategy analysis is able to show whether the person uses a holistic approach or a fragmented approach by using a scoring system assessing good continuity and good connection. A recent study showed no sex difference on the strategy in young Japanese people (Sakamoto, 2006); therefore it is possible that the sex differences among the Japanese elderly may be also diminished. By analyzing strategy, it will help to better understand how Japanese AD and VaD patients differently approach the ROCFT.

Unlike the ROCFT or Clock Drawing, the Judgment of Line Orientation Test (JOLO) assesses pure visuospatial ability governed by the right hemisphere (Lezak, 2004). Adding the JOLO will reveal whether the impairment in spatial abilities is due to purer spatial orientation deficit.

Thus, by including different types of spatial performance tests (i.e. JOLO, ROCFT, and Clock Drawing), it will be able to assess which aspects of spatial abilities are impaired or intact (i.e. purely spatial ability, spatial planning, spatial organization).

Executive Functioning Tests

Digit Span Backward Task is used to assess working memory, which is a part of executive/ frontal process. Persons with VaD usually have disadvantages on the test because of an inability to establish and maintain the mental sets (Cosentino et al., 2004; Lamar et al., 2004; Libon et al., 2004). A Japanese fNIR study reported that individuals who outperformed on the Digit Span Backward Task showed significantly more blood flow in frontal lobe (Hoshi, et al., 2000). If the Japanese VaD patients have impairments in executive control, it is more likely to observe reduced blood flow in frontal lobe as well as significantly lower scores on the Digit Span Backward Task. This task is easily administered and accurately demonstrates the dysexecutive syndrome of VaD (Oosterman and Scherder, 2003). It is suggested that the Digit Span Backward Task can differentiate Japanese AD and VaD as well as American AD and VaD.

Both ROCFT and Clock Drawing Test are also assessments for executive control abilities because they examine abilities of spatial planning and inhibition. Japanese persons on average have strong spatial abilities because of their unique written language, so it is crucial to assess frontal and executive control in the visuospatial domain. It is important to note that the ROCFT can be a useful test for patients with mild dementia;

however it may not be valid for patients with moderate to severe dementia because ROCFT may be too difficult to even copy for persons with more severe dementia.

Wisconsin Card Sorting Test (WCST) is a powerful and well established test to assess one's executive control abilities. However, it is lengthy and complicated; therefore, it may not be considered an easy and quick test for elderly individuals. The target population in dementia research is older adults; therefore, they become tired faster than young adults. As time is of the essence, it is crucial to quickly complete testing in order to obtain valid results (Tei et al., 1997). The Japanese study used the WCST and successfully differentiated Japanese VaD from AD; however, it is still questionable if it is an appropriate test for very old Japanese.

Information Processing Speed Tests

Information processing speed is often assessed by Digit Symbol (DS) and Digit Copy (DC) Test. Motor slowness and perseveration errors that VaD patients often make are usually key elements in differentiating VaD from AD (Sakamoto et al., 2007). How Japanese elders, especially those with VaD, perform on the DS and DC is unknown; however, it is possible that Japanese VaD may not perform as badly as western VaD because the DS and DC consist of symbols. The Japanese written language, Kanji, is a set of pictorial symbols. Because Japanese elders have been exposed to the symbolic characters throughout their life, the experience may prevent the Japanese elders from slowing down or making errors on those tests. It would be interesting if Japanese AD and VaD patients perform similarly on the tests. Therefore, it is believed that the DS and DC are appropriate tests to assess two Japanese dementia groups.

Language Tests

Letter Fluency and Semantic Fluency Tests are commonly used in Japanese dementia studies (Takahashi, et al., 2006). Japanese AD patients tend to perform more poorly than healthy controls on semantic fluency tasks (Takahashi et al., 2007). It is not well studied how Japanese VaD perform differently as compared to the Japanese AD on the letter and semantic fluency tests; therefore it is difficult to propose that the verbal and semantic fluency tests will differentiate Japanese AD and VaD. However, it is worthwhile to explore if they can be useful assessment tools for Japanese dementia studies as a first attempt to choose sensitive and appropriate tests for Japanese culture.

Memory Tests

In Japanese dementia studies, subtests of the WMS are often used to assess memory functions (Kazui, Hashimoto, Hirono, & Mori, 2003). However, recent studies conducted by western researchers suggest that verbal learning tests (e.g. CVLT and PrVLT) are powerful assessment tools that demonstrate that AD has more encoding problems whereas VaD has more retrieval problems (Lamar et al., 2007; Libon et al., 1996; Looi & Sachdev, 1999). There is no Japanese study examining the usability and validity of a verbal learning test for the dementia population. There is Japanese Verbal Learning Test 16 item version (JVLT-16) just developed in 2006 by Dr. Matsui to assess memory function of schizophrenia patients (Matsui et al., 2006). However, the JVLT-16 has only three trials in a new learning phase and no recognition index (Matsui et al., 2006). Western clinicians use 9-item version in dementia clinics, as it is too difficult to have 16 words for dementia patients. Furthermore, the JVLT-16 is not normed among the elderly. Therefore, the Japanese Verbal Learning Test (PVLT-J) has been developed for the Japanese elders. It was carefully structured and modified based on PrVLT and CVLT with supervision from Dr. Libon and Dr. Matsui who developed the PrVLT and JVLT-16 respectively. Impairment in episodic memory is a prominent deficit of AD; therefore, it is crucial to try the verbal learning test for Japanese elders.

Summary

In summary, this study is the first study trying to find appropriate neuropsychological tests which are able to differentiate AD and VaD among Japanese elders with great consideration of cultural differences. Because accurate diagnosis and early treatment may prevent the progression of the disease, it is important to better understand what neuropsychological tests are the most sensitive and efficient to successfully differentiate VaD and AD and how these groups perform similarly or differently on the tests. It has been suggested that there are more VaD than AD in Japan. VaD is preventable and treatable at the early stage of the disease; therefore, this study will provide new information regarding what cognitive domains are important and what kinds of cognitive impairments will possibly emerge when a patient shows VaD syndrome.

Japan has the longest life expectancy and largest aging society in the world. Dementia is therefore a serious problem in Japan. In order for Japanese elders with dementia and their families to have a better quality of life, it is Japanese clinicians' responsibilities to diagnose accurately and develop effective treatment plans in the initial or prodromal stage. It is vital to better understand how AD and VaD affect Japanese elders' cognitive functions for successful treatments.

CHAPTER 2. HYPOTHESES

It was hypothesized that visuospatial assessments would add helpful information regarding different performance on cognitive testing between Japanese AD and VaD patients. Five overall hypotheses were derived from the results of previous studies:

1. VaD patients would perform worse on visuospatial tasks than AD patients.
2. VaD patients would perform worse on executive control ability tasks than AD patients.
3. VaD and AD patients would perform similarly on tasks of information processing speed.
4. AD patients would perform worse on delayed recall and recognition trials for both verbal and non-verbal memory tasks than VaD patients.
5. AD patients would perform worse on language tasks than VaD patients.

Because it is unknown how healthy Japanese elders would perform on the specific neuropsychological assessments, healthy controls were also recruited in this study. It was important to compare those diagnostic groups to the healthy control group. One study has demonstrated smaller magnitude of sex differences in Japanese young group compared to Japanese American and European American group (Sakamoto, 2006); therefore, it was also examined whether or not the smaller sex differences would be found between Japanese healthy men and women in the control group. It was hypothesized overall that the Japanese old men and women would perform similarly on neuropsychological tests, especially visuospatial tasks and verbal fluency tasks.

CHAPTER 3. METHOD

3.1. Participants

Seventy Japanese (30 healthy control, 20 AD patients, and 20 VaD patients) participants were recruited to the current study. The number of participants was determined by power analysis. Effect sizes of the neuropsychological tests which were used in this study were calculated based on the previous western studies and Tei et al.'s study (Tei et al., 1997). The range of the effect sizes were between d = 0.23 (Animal Naming Test) and d = 1.90 (ROCFT). Twelve dependent variables showed a large effect size; therefore, the effect size to determine the number of participants was set at a large effect size, which is 0.4. A p-value was set at 0.05, 1-tailed. The Sample Power program of the SPSS indicated that at least 20 people would be necessary in each group to obtain an ideal power, 0.8. When 20 people are recruited in each group, the power is 0.78.

It is well documented that age and education impact performance on neuropsychological testing. Age and education were matched among healthy controls, AD, and VaD groups.

In general, approximately 80% of dementia patients are female; therefore, it was expected that the majority of the participants in AD and VaD group would also be female; however, the same number of males and females were successfully recruited into each group.

Sex differences were examined in healthy controls; therefore 30 participants (15 males and 15 females) were recruited. Regardless of diagnostic groups, the individuals were required to meet the general inclusion and exclusion criteria as described below.

3.1.1. General Inclusion/ Exclusion Criteria for All Participants

To be eligible to participate in the study, individuals needed to be (a) between 65 and 85 years old; (b) able to read in Japanese, (at least at a ninth-grade level); and (c) willing to provide written informed consent and demographic information. The reading level was set at the ninth-level because the majority of basic Kanji characters used in daily life are taught by the ninth-grade in school. A brief Kanji test was given to all participants to assess their reading level as well as the level of their knowledge of Kanji.

Individuals who (a) were left handed, (b) had neurological or psychological disorders (other than dementias for individuals in dementia groups), and (c) obtained 79 or fewer points on the Kanji reading test were excluded from participation. All participants passed this Kanji test. Only right-handed individuals were recruited to this study to maintain homogeneity within and between groups. The Beck Depression Inventory (BDI), which is also available in Japanese, was administered to exclude people who were clinically depressed. Individuals who obtained 20 or higher score on the BDI would have been excluded from the current study; however, all participants scored less than 20.

3.1.2. Inclusion/Exclusion Criteria for Participants in Healthy Control Group

Individuals in the healthy control group scored 26 or higher on the Hasegawa Mini Mental Status Examination (MMSE) (Folstein et al., 1975; Tei et al., 1997). There are variations of MMSE scores to define "normal controls". The score 26 or higher for healthy controls was determined based on the Japanese studies that used the Hasegawa MMSE for Japanese elders (Tei et al., 1997; Koga et al., 2007).

3.1.3. Inclusion Criteria for Patients with Dementias

Individuals in the dementia group were diagnosed with AD or VaD by clinicians and neurologists based on CT scan and/or MRI film and medical history, such as cardiovascular disease, prior to the study. For the purpose of the current study, patients with mild dementia were recruited for internal validity; therefore, they had to score between 18 and 24 on the Hasegawa MMSE. Scores between 18 and 24 on the Hasegawa MMSE are considered to be indicative of mild cognitive impairment (Kato et al., 1991; Koga et al., 2007).

3.1.4. Subject Recruitment

3.1.4.1. Healthy Controls

The healthy Japanese participants were recruited using flyers posted at Nanpu hospitals and Nara Women's University in Nara prefecture, Japan. The flyers provided contact information so that individuals who were interested in this study were able to reach the researcher for an appointment. During the first phone contact with potential participants, the researcher asked questions regarding their age, handedness, and medical and psychological history to decide if the interested persons were eligible for this study. The BDI was also given to them orally during the first phone contact. When the persons fit all of the inclusion criteria, they were invited to the study. Since there was no compensation involved, the researcher went to each participant's residence to administer the protocol.

3.1.4.2. Participants with Dementias

The patients with AD or VaD were recruited at Nanpu hospitals in Nara, Japan. Nanpu hospitals have four different care units for the elders with dementia and other mental and medical problems. The neurologists and clinicians at the Nanpu hospital made the initial diagnosis of dementia based on the DSM-IV-TR criteria, the score on the Mini-Mental State Examination (MMSE), and medical history. Then, they made the diagnoses of VaD using NINDS-AIREN criteria and AD using the NINCDS-ADRDA criteria. For the purpose of this study, only patients with probable VaD were included. The computed tomography (CT) and Magnetic Resonance Imaging (MRI) studies were also reviewed to support the diagnosis. Based on the diagnosis, a list of possible participants' names was given to the researcher, and she contacted each patient. The BDI was given to the patients during the first meeting. The researcher then asked the patients who met the inclusion criteria and their families whether they were interested in participating in this study. The Japanese culture is strongly family oriented; therefore, it was important to assure not only the patient's consent, but also their families' agreement to participate in this study. When the patients and their families agreed to participate, the researcher explained the informed consent.

3.2. Measures

The neuropsychological assessments used in this study were part of a harmonized protocol chosen by the National Institute of Neurological Disorders and Stroke and the Canadian Stroke Network in order to successfully diagnose VaD and VaD related cognitive impairments (Hachinski et al., 2006). In the current study, memory, executive function, working memory, information processing speed, visuospatial construction abilities, and language/semantic knowledge were tested. These domains were examined because previous studies demonstrated unique and different clinical presentations between AD and VaD (Hachinski, et al., 2006; Price et al., 2005; Libon et al., 2008; Looi & Sachdev, 2003). Analysis of types of errors were also helpful to understand the strengths and weaknesses of those patients with dementia (Giovannetti, Lamar, Grossman, Cloud, & Libon, 1997; Jorm, et al., 1993; Libon et al., 2004; McPherson & Cummings, 1996; Sachdev & Looi, 2003). Each test in each cognitive domain were listed and explained below.

Hasegawa Mini-Mental State Examination (MMSE): The MMSE is a general cognitive screening test that measures orientation, language, concentration, constructional praxis, and memory (Folstein, Folstein, & McHugh, 1975). The maximum score on the test is 30. The MMSE has been translated, and modified by Dr. Hasegawa, and is commonly used for dementia in Japan (Hasegawa, 1983; Koga et al., 2002; Yoshitake et al., 1996). The Japanese version of the MMSE, the Hasegawa MMSE, was administered to the Japanese participants. The Hasegawa MMSE was used to match two diagnostic groups as overall cognitive levels, AD and VaD.

<u>Executive Control</u>

Digit Span Backward Task (Lamar et al., 2007, 2008): Working memory abilities require a significant capacity of performing a mental manipulation. Therefore, working memory is usually thought to be a part of executive control mechanism. This skill of working memory were assessed by the Digit Span Backward Task consisting of 3-, 4-, and 5-span trials. The Digit Span Backward Task is similar to the Digit Span Backward subtest of Wechsler Adult Intelligence Scale (WAIS) and Wechsler Memory Scale (WMS); however, it has more trials in each span to assess specific components of the working memory (Lamar et al., 2007, 2008). Unlike the Digit Span Backward subtest of the WAIS or WMS, the Digit Span Backward Task focuses on not only accuracy but also the types of errors that one makes. On this task, the participants were asked to repeat increasingly lengthy strings of numbers in reverse order. The “Any Order” and “Serial Order” suggest if the working memory impairment is due to storage or mental manipulation impairment, which indicates the inability to retain the necessary information in mind, or because of a true inability to mentally manipulate information as demanded by the task. The Any Order scoring is to give points for answers that have numbers that were said but may not be in the right order. The Serial Order scoring is to give points for only answers that have numbers in the correct order. These two scoring systems were the dependent variables for the test.

Information Processing Speed

Digit Symbol (DS) and Symbol Copy (SC) Test (WAIS-R-NI; Kaplan et al., 1987): On the DS test, there are numbers from “1” to “9” and each number has one symbol. These symbols are presented at the top of the test as a model. Under the model, only numbers are presented in boxes with blank boxes underneath. The participants were asked to fill out each empty box with a symbol that is associated with the specific number presented just above the box. The participants were asked to try to fill out as many boxes as possible in 120 seconds. The DS test is a sensitive tool to detect dementia because patients show decline on this test even in early stages of the diseases (Strandt & Hill, 1989: Lezak, 2004). On the SC test, the participants were asked to copy a symbol presented just above the empty box in 120 seconds. The SC is useful to distinguish between AD and VaD since VaD patients do not improve their performance on the SC from the DS tests due to their bradykinesia (slow movement; Sakamoto et al., 2007). For each test, the dependent variable was the number of correct items completed.

Visuospatial Construction

Clock Drawing Test: This test is useful for assessing one's visuospatial construction as well as executive control abilities. The participants were asked to draw a face of a clock to command and to copy with hands set for 10 after 11 (Goodglass & Kaplan, 1986). The performance was scored based on 10 errors. Those 10 errors can be placed into three categories: graphomotor impairments, hand and number placement, and executive control impairments (Libon et al., 1996). This test is considered to be sensitive to frontal-subcortical impairment (Cosentino et al., 2004; Libon et al., 1996). The dependent variable for the Clock Drawing Test was the number of errors.

Judgment of Line Orientation test-short form (JOLO): This test is to examine the ability to estimate angular relationships between line segments by visually matching angled line pairs to nine numbered radii forming a half circle. The test consists of twelve items (Libon et al., submitted). The participants were asked to scan and find the same angle as the model. They were asked to only point out the line without speaking in order to avoid a verbal component. Studies have showed that the JOLO is able to assess pure spatial ability governed by the right hemisphere (Lezak, 2004). The dependent variable was the number of correct answers.

<u>Language/ Semantic Knowledge</u>

Letter Fluency Test: The Letter Fluency Test was originally developed by Benton and his colleagues in the U.S. (Spreen & Benton, 1969). This test was originally developed to assess a person's executive control ability because s/he has to inhibit unwanted information and produce only the necessary response. "F", "A", and "S" are the most commonly used letters for fluency test. In Japan, "し (shi)", "い (i)", and "れ(re)" are the most widely used (Takahashi et al., 2007). This procedure is an oral form and the participants were asked to say words that begin with a specified letter as many as in three trials of 60 seconds each. The verbal fluency test is widely used by neuropsychologists since it is one of the most useful instruments as it is sensitive to frontal involvement, especially left-frontal lobe damage (Benton, 1968). The dependent variable was the total number of correct responses summed across all three trials.

Animal Naming Test: Animal Naming Test is one of the most useful tests to assess semantic knowledge (Carew et al., 1997). On this task, the participants were asked to produce as many animal names as they can think of in 60 seconds. The successful number of responses was the dependent variable. Many studies demonstrated that VaD scored higher than AD (Henry, Crawford & Phillips, 2004; Monsch et al., 1997). The dependent variable for the Animal Naming Test was the number of correct items completed.

<u>Learning and Memory</u>

Philadelphia (repeatable) Verbal Learning Test-Japanese Version (PVLT-J): The Japanese version of verbal learning test was developed based on the Philadelphia (repeatable) Verbal Learning Test (PrVLT) and the 9-word experimental version of the CVLT (CVLT-9; Davis et al., 2002; Libon et al., 1996) for the purpose of this study. Some items (i.e. cauliflower and lamb) and categories (i.e., meat) on the CVLT-9 or P(r)VLT are less familiar to the Japanese elders; therefore, those items and categories were eliminated from the PVLT-J. Fifty seven Japanese individuals aged between 31 and 82 were asked to report most familiar and common items in each category including vegetables, fruits, fish, flowers, clothing, desserts, office supplies, tools, and furniture. Based on their responses, second most frequently answered items (55-75% of answers) were chosen for the actual items on the PVLT-J. Most frequently answered items (75% or higher) were used in the recognition trial as "prototypical items".

This test has two forms, and each contains nine words which are drawn from three semantic categories. The participants were asked to repeat each word after the examiner said it. After all nine words were said, the participants were asked to recall as many words as they can remember. When five trials were completed, a different 9-word interference list was then administered. This second list is interference; therefore, it was given only one time. Then the participants were asked to recall all of the words from the original list followed by a category cued recall condition. After completing delayed free and cued recalls, the participants were asked to answer "yes" or "no" if the words were from the first list. There were 36 items in the recognition trial. Short and delayed free and category recall for the original list and delayed recognition were assessed.

Rey-Osterrieth Complex Figure Test (ROCFT): The ROCFT is able to measure not only visuospatial ability but also visuospatial memory in ages 6-89 years (Meyers & Meyers, 1995). The ROCFT was selected to use in this study because the Japanese study showed its value in differentiating AD and VaD (Tei et al., 1997). The ROCFT has three parts: Copy, Immediate Recall, and Delay Recall. Participants were exposed to a figure and copied it on a blank sheet (Copy). After the figure was taken away from the participants, they were asked to draw the figure from their memory (Immediate Recall). Then, 20 minutes later, the participants were again asked to recall and produce the picture on another blank sheet (Delay Recall). The results from the Immediate Recall and Delayed Recall were scored by accuracy. Accuracy was scored with an 18 criteria system (accuracy of the angles, correctness of proportions, etc.) and scores were given for distortion and for placement (Bennet-Levy, 1984; Meyers & Meyers, 1995). A maximum of two points (one for accuracy and one for placement) was allocated to each scoring unit so that the highest possible score was 36. The results from the Copy were scored by strategy (Bennet-Levy, 1984). The participants' approach and strategies to draw the picture were monitored. The more holistic the approach used, the more points were awarded towards strategy. The maximum score for strategy was also 36.

In addition to the neuropsychological tests, demographic information was obtained from the participants at the beginning of testing. The questions included age, date of birth, years of education, occupation, and medical and psychological history. The data were confidential and used only to examine whether or not there were significant differences between groups.

3.3. Setting

3.3.1. Participants in Healthy Control Group

The examiners visited the participants' residences to administer the protocol.

3.3.2. Japanese Patients with Dementia

All patients stayed at the assisted care unit of the Nanpu hospitals. The patients were scheduled to come to the laboratory room in the Nanpu hospitals to complete the testing.

3.4. Procedure

Regardless of the difference in location of testing, all participants underwent the same procedure. There was one demographic questionnaire and eight neuropsychological tests. Prior to testing, all participants were asked to carefully read the informed consent form and to sign it if they agreed to participate in this study. The tests and questionnaires were administered in this order:

Mini-Mental Status Exam (MMSE)
Demographic Questionnaire

1. Clock Drawing test
2. PVLT-J
3. ROCFT – Copy and Immediate Recall
4. Digit Span Backward Task
5. Digit Symbol and Symbol Copy Test
6. JOLO
7. PVLT-J – Delayed condition and recognition test
8. ROCFT – Delayed Recall
9. Letter Fluency Test
10. Animal Naming Test

This protocol took approximately one hour to complete.

3.5. Data Analysis

There was one independent variable with three levels: Diagnosis (AD vs. VaD vs. healthy control); therefore, the statistical analysis was a between group design. Twenty three dependent variables were analyzed using multivariate analysis of variance (MANOVA) to decrease type I errors. When there were significant main effects, Tukey's post hoc tests were conducted in order to determine which groups were significantly different. Effect sizes of each analysis were also calculated.

As a second analysis, sex differences in healthy controls were examined. A MANOVA were conducted to examine whether or not small sex differences were found in Japanese elderly group. SPSS 16.0 (SPSS, Inc.) was used in all analyses, and all values were considered significant at $p < .05$ (two-tailed).

CHAPTER 4. RESULTS

4.1. Participant Demographic Characteristics

Seventy participants (20 Alzheimer patients, 20 vascular dementia patients, and 30 healthy controls), were recruited in this study. The original 70 elders who were contacted by the researcher participated in this study and no one declined after reading and signing the consent form. Demographic data are presented in table 3.1. No significant differences in age, years of education, and Beck Depression Inventory (BDI) scores were observed [Age: $F(2, 69) = 2.56$, $p = .09$, Education: $F(2, 69) = .02$, $p = .40$, BDI: $F(2, 69) = .36$, $p = .70$]. While there was a significant difference in MMSE between the healthy control group (HC) and the other two diagnostic groups [$F(2, 69) = 243.24$, $p < .001$], as was expected, there was no difference in MMSE scores between Alzheimer's disease (AD) and vascular dementia (VaD) group [HC vs. AD ($p < .001$), HC vs. VaD ($p < .001$), AD vs. VaD ($p = .33$)].

Table 4.1. Demographic data (Age, Education, BDI, and MMSE)

	HC	AD	VaD	
	Mean (SD)	Mean (SD)	Mean (SD)	
Age	75.0 (4.68)	77.7 (4.42)	77.1 (4.26)	
Education	12.6 (2.57)	11.7 (2.74)	11.5 (2.59)	
BDI	6.9 (4.61)	7.9 (4.23)	7.6 (3.91)	
MMSE*	29.3 (.88)	20.1 (2.13)	20.9 (2.01)	†

* $p < .001$
† HC vs. AD ($p < .001$), HC vs. VaD ($p < .001$)

4.2. Test Results

A multiple analysis of variance (MANOVA) was conducted in order to examine main effects for diagnosis (HC vs. AD vs. VaD). When significant differences were found, Tukey's HSD post hoc tests were executed to identify which two groups had a difference. A partial eta squared was also provided to demonstrate an effect size for each result.

Executive Control

4.2.1. *Digit Span Backward Task*

Table 4.2 provides means and standard deviations for each group. The MANOVA revealed that there was no significant difference for the 3-span Any Order trial [$F(2, 69) = 1.42$, $p = .250$, $\mu^2 = .04$] while for the 3-span Serial Order trial, a significant difference was found [$F(2, 69) = 4.10$, $p = .020$, $\mu^2 = .11$]. The post hoc tests revealed that the HC group produced the numbers more accurately than the AD group ($p = .02$) and the VaD group ($p = .02$). There was no significant difference between AD and VaD groups ($p = .91$).

In terms of 4-span trials, there was no significant difference between three groups for the Any Order trial [$F(2, 69) = 1.65$, $p = .20$, $\mu^2 = .05$] while a significant difference was found for the Serial Order trial [$F(2, 69) = 5.42$, $p = .007$, $\mu^2 = .14$]. The post hoc tests revealed that the HC group produced more numbers in a correct order than the AD group ($p = .002$) and the VaD group ($p = .04$). There was no significant difference between AD and VaD groups ($p = .30$).

There were significant differences on both the 5-span Any Order and Serial Order trials [Any Order: $F(2, 69) = 3.75$, $p = .03$, $\mu^2 = .10$, Serial Order: $F(2, 69) = 10.77$, $p < .001$, $\mu^2 = .25$]. For the Any Order trial, there was a significant difference only between HC and AD groups ($p = .008$). The HC group and VaD group did not show a significant difference ($p = .23$). No significant difference was detected between the AD and VaD group, either ($p = .34$). On the Serial Order trial, there were significant differences between HC and AD groups ($p < .001$) and between HC and VaD groups ($p = .005$); however, the AD and VaD groups performed similarly ($p = .57$).

The Digit Span Backward Task is considered to be a sensitive task, especially the Serial order trials, to detect dementia. It was hypothesized that the VaD patients would perform worse on executive control ability tasks than the AD patients; however, even the toughest task, 5-span Serial order trial, was not able to differentiate between AD and VaD groups.

Table 4.2. Group means (%) and standard deviations of Digit Span Backward Task

		HC	AD	VaD	
		Mean (SD)	Mean (SD)	Mean (SD)	
3-span	Any	99.2 (2.31)	100 (0)	99.3 (1.83)	
	Serial*	94.0 (8.67)	84.2 (14.45)	83.6 (20.84)	†
4-span	Any	94.9 (6.31)	96.7 (5.78)	97.8 (4.75)	
	Serial**	81.9 (17.83)	66.2 (15.97)	71.8 (16.85)	††
5-span	Any*	89.6 (8.29)	82.4 (10.86)	86.5 (8.78)	†††
	Serial**	70.1 (16.54)	48.7 (16.36)	54.2 (18.57)	††††

*$p < .05$, **$p < .001$,
† HC vs. AD ($p = .02$), HC vs. VaD ($p = .02$)
†† HC vs. AD ($p = .002$), HC vs. VaD ($p = .04$)
††† HC vs. AD ($p = .008$)
††† HC vs. AD ($p < .001$), HC vs. VaD $p = .005$)

<u>Information Processing Speed</u>

4.2.2. *Digit Symbol (DS) and Symbol Copy (SC) Test*

Table 4.3 provides means and standard deviations for each group. The MANOVA revealed that there were significant differences on the Digit Symbol Test [$F(2, 69) = 187.78$, $p < .001$, $\mu^2 = .85$]. The post hoc tests revealed that the HC group drew more symbols than the AD group ($p < .001$) and the VaD group ($p < .001$); however, there was no significant difference between the AD and VaD groups ($p = .979$). A similar result was found in the Symbol Copy test. There was a difference at least between two groups

[$F(2, 69) = 172.55$, $p < .001$, $\mu^2 = .84$]. The HC groups copied significantly more symbols than the AD group ($p < .001$) and the VaD group ($p < .001$); however, there was no significant difference between the AD and VaD groups ($p = .39$). The hypothesis that the AD and VaD groups would perform similarly was supported.

Table 4.3. Group means (%) and standard deviations of Digit Symbol and Symbol Copy Tests

	HC	AD	VaD	
	Mean (SD)	Mean (SD)	Mean (SD)	
Digit Symbol**	61.1 (13.54)	14.9 (4.41)	15.5 (5.17)	†
Symbol Copy**	113.23 (24.31)	32.9 (13.00)	23.5 (10.21)	††

** $p < .001$
† HC vs. AD ($p < .001$), HC vs. VaD ($p < .001$)
†† HC vs. AD ($p < .001$), HC vs. VaD ($p < .001$)

Visuospatial/Construction

4.2.3. *Clock Drawing Test*

There were two trials on the Clock Drawing Test: Command and Copy trials. Table 4.4 provides means and standard deviations for each group. The MANOVA revealed that there was significant differences on the Command trial of the Clock Drawing Test [$F(2, 69) = 13.23$, $p < .001$, $\mu^2 = .28$]. The post hoc tests demonstrated that the HC group drew a face of a clock more accurately from their memory than the AD group ($p = .013$) and the VaD group ($p < .001$). The AD and VaD groups made similar number of errors ($p = .137$). On the Copy trial, the MANOVA showed that there were significant differences [$F(2, 69) = 16.53$, $p < .001$, $\mu^2 = .33$]. The HC groups copied the face of a clock on the sheet more accurately than the AD group ($p = .002$) and the VaD group ($p < .001$). Like the Command trial, there was no significant difference between the AD and VaD groups (p = .151). The hypothesis that the VaD group would make more errors on the Clock Drawing test was not supported.

Table 4.4. Group means and standard deviations of Clock Drawing Test

	HC	AD	VaD	
# of errors	Mean (SD)	Mean (SD)	Mean (SD)	
Command**	0.53 (0.68)	1.50 (0.95)	2.20 (1.73)	†
Copy**	0.0 (0)	.85 (.88)	1.35 (1.31)	††

** $p < .001$
† HC vs. AD (p = .013), HC vs. VaD ($p < .001$)
†† HC vs. AD (p = .002), HC vs. VaD ($p < .001$)

4.2.4. *Judgment of Line Orientation test-short form (JOLO)*

Table 4.5 provides means and standard deviations for each group. On this test, a percentage of the correct answer was used as a score. Significant differences on the JOLO were found [$F(2, 69) = 19.82$, $p < .001$, $\mu^2 = .37$]. The post hoc tests revealed that the HC group was able to identify correct lines more accurately than the AD group ($p < .001$). Interestingly, the individuals in the VaD group were similarly able to point out the correct lines as the HC group; as a result, no significant difference between HC and VaD groups was found (p = .19). Additionally, the VaD group performed significantly better than the AD group ($p < .001$). The JOLO, a pure spatial/constructional task, was able to differentiate between the AD and VaD.

Table 4.5. Group means and standard deviations of JOLO

	HC	AD	VaD	
Accuracy(%)	Mean (SD)	Mean (SD)	Mean (SD)	
JOLO**	98.4 (5.04)	70.3 (26.22)	90.5 (11.33)	†

** $p < .001$
† HC vs. AD ($p < .001$), AD vs. VaD $p < .001$)

In summary for visuospatial/construction tasks, it was hypothesized that the VaD patients would perform worse than the AD patients; however, this study found that both groups performed similarly. The hypothesis was not supported; moreover, VaD patients performed better on the pure spatial task, JOLO, than AD patients.

Language/ Semantic Knowledge

4.2.5. *Letter Fluency Test*

Table 4.6 provides means and standard deviations for each group. The MANOVA revealed that there was a significant difference on the letter fluency test [$F(2, 69) = 44.55$, $p < .001$, $\mu^2 = .57$]. The post hoc tests revealed that the HC group produced more words than the AD group ($p < .001$) and the VaD group ($p < .001$). There was no difference between the AD and VaD groups ($p = .14$). The AD and VaD patients produced a similar numbers of words that begin with a certain letter of alphabet within 60 seconds.

Table 4.6. Group means and standard deviations of Letter Fluency and Animal Naming Test

	HC	AD	VaD	
	Mean (SD)	Mean (SD)	Mean (SD)	
Letter Fluency**	27.4 (6.52)	12.7 (5.67)	16.2 (4.71)	†
Animal Naming**	18.4 (4.06)	7.1 (2.83)	9.8 (2.84)	††

** $p < .001$
† HC vs. AD ($p < .001$), HC vs. VaD ($p < .001$)
†† HC vs. AD ($p < .001$), HC vs. VaD ($p < .001$)

4.2.6. *Animal Naming Test*

Table 4.6 above provides means and standard deviations for each group. There was a statistically significant difference between two groups on the Animal Naming performance [$F(2, 69) = 81.75$, $p < .001$, $\mu^2 = .71$]. The post hoc tests indicated that the

HC group produced more animal names than the AD group ($p < .001$) and the VaD group ($p < .001$); however, the patients in the AD group and VaD group performed similarly. No significant difference was found between the AD and VaD groups ($p = .10$); however, it can be considered that there was a trend that VaD produced more animal names than AD patients.

In summary, the hypothesis that the AD patients would perform worse than the VaD patients on language tasks was rejected by this study. The AD and VaD patients produced similar numbers of words on both verbal and animal fluency tests; although there was a trend that AD patients produced fewer words than VaD patients on the semantic fluency task.

Learning and Memory

4.2.7. *Philadelphia (repeatable) Verbal Learning Test-Japanese Version (PVLT-J)*

On the PVLT-J, performances on the six trials were statistically analyzed, which were: 1) a total number of words T1 to T5 (Total T1-5), 2) Short Delay Free Recall (SDFR), 3) Short Delay Cued Recall (SDCR), 4) Long Delay Free Recall (LDFR), 5) Long Delay Cued Recall (LDCR), and 6) Recognition.

Table 4.7 provides means and standard deviations for each group. The MANOVA demonstrated that there was a significant difference on the Total T1-5 [$F(2, 69) = 107.46$, $p < .001$, $\mu^2 = .764$]. The post hoc tests showed that the HC group recalled more words than the AD group ($p < .001$) and the VaD group ($p < .001$); however, the AD group and VaD group did not perform differently ($p = .30$). On the SDFR, a significant difference was found [$F(2, 69) = 57.22$, $p < .001$, $\mu^2 = .635$]. The HC group produced more words from the Monday list than the AD ($p < .001$) and the VaD groups ($p < .001$). There was no significant difference between AD and VaD groups ($p = .866$). On the SDCR, there was also a significant difference between two groups [$F(2, 69) = 54.71$, $p < .001$, $\mu^2 = .627$]. The post hoc tests demonstrated that the HC was able to recall more words after the interference than the AD ($p < .001$) and VaD ($p < .001$). Like the SDFR, there was no significant difference between the AD and the VaD groups ($p = .27$). There was also a significant difference on the LDFR [$F(2, 69) = 132.48$, $p < .001$, $\mu^2 = .797$]. The HC group recalled more words from the Monday list after the 20-minute delay than the AD ($p < .001$) and VaD ($p < .001$). The patients with AD and VaD recalled similar numbers of words on the LDFR ($p = 1.00$). On the LDCR trial, a significant difference was found [$F(2, 69) = 133.70$, $p < .001$, $\mu^2 = .797$]. The HC performed better than the AD ($p < .001$) and VaD ($p < .001$) and moreover, the VaD group recalled more words than the AD by given cues ($p = .008$). The patients in the VaD group benefited from cues while AD did not. Lastly, on the recognition, there was a significant performance difference [$F(2, 69) = 30.72$, $p < .001$, $\mu^2 = .480$]. The HC group identified more correct items that were on the Monday list than the AD ($p < .001$) and VaD ($p < .001$) groups. As with the LDCR, the VaD patients were able to more successfully identify the Monday items than the AD patients ($p < .001$).

As it was hypothesized, the VaD patients benefited from cues during the long delay and recognition trials. The VaD patients performed significantly better than the AD patients on long delayed recall and recognition trials of the PVLT-J.

Table 4.7. Group means and standard deviations of PVLT-J

	HC	AD	VaD	
	Mean (SD)	Mean (SD)	Mean (SD)	
Total T1-T5**	35.8 (4.27)	19.1 (4.14)	21.2(4.88)	†
SDFR**	6.5 (2.05)	1.6 (1.57)	1.9 (1.81)	††
SDCR **	7.6 (1.17)	3.05 (2.04)	3.8 (1.76)	†††
LDFR**	7.3 (1.54)	1.3 (1.59)	1.3 (1.49)	††††
LDCR**	7.8 (1.22)	2.0 (1.34)	3.0 (1.61)	†††††
Recognition (%)**	95.9 (5.02)	72.1(15.84)	87.3(10.06)	††††††

** $p < .001$
† HC vs. AD ($p < .001$), HC vs. VaD ($p < .001$),
†† HC vs. AD ($p < .001$), HC vs. VaD ($p < .001$)
††† HC vs. AD ($p < .001$), HC vs. VaD ($p < .001$)
†††† HC vs. AD ($p < .001$), HC vs. VaD ($p < .001$)
††††† HC vs. AD ($p < .001$), HC vs. VaD ($p < .001$), AD vs. VaD ($p = .008$)
†††††† HC vs. AD ($p < .001$), HC vs. VaD ($p < .001$), AD vs. VaD ($p < .001$)

4.2.8. *Rey-Osterrieth Complex Figure Test (ROCFT)*

The ROCFT had four trials: Copy, Immediate Recall (IR), Delayed Recall (DR), and Strategy. Copy, IR and DR measured accuracy, and Strategy evaluated one's approach for drawing the complex figure. The means and the standard deviations can be found in the Table 4.8. The MANOVA revealed that there was a significant difference on the Copy trial [$F(2, 69) = 20.12$, $p < .001$, $\mu^2 = .375$]. The HC group copied the figure more accurately than the AD group ($p < .001$) and VaD group ($p < .001$). Also, there was a significant performance difference between the AD and VaD groups ($p = .05$). This showed that the patients with VaD copied the figure more accurately than the patients with AD. There was also a significant difference on the IR [$F(2, 69) = 49.00$, $p < .001$, $\mu^2 = .594$]. The post hoc tests showed that the HC group scored better in accuracy on the IR than the AD ($p < .001$) and the VaD groups ($p < .001$). Additionally, the patients with VaD performed better than the patients with AD group ($p = .02$). The VaD patients recalled the complex figure more accurately than the AD patients. On the DR, a significant difference was also found [$F(2, 69) = 66.62$, $p < .001$, $\mu^2 = .665$]. The HC group recalled better than the AD group ($p < .001$) and the VaD group ($p < .001$). As with the IR, the VaD group recalled more than the AD group ($p = .006$). Twenty minutes later, the AD patients barely remembered the figure. Three patients with AD could not remember that they had copied the figure earlier. The scores on the Strategy were drawn from the Copy trial. There was also a significant difference between two groups [$F(2, 69) = 26.37$, $p < .001$, $\mu^2 = .440$]. The post hoc tests revealed that the HC used a more holistic approach than the AD group ($p < .001$) and VaD group ($p < .001$). Interestingly, the VaD patients performed better on the Strategy than the AD patients ($p < .03$). Not only the Accuracy (Copy, IR and DR), but also the Strategy drawn from Copy trial demonstrated their sensitivity to differentiate between AD and VaD.

Table 4.8. Group means and standard deviations of ROCFT

	HC	AD	VaD	
	Mean (SD)	Mean (SD)	Mean (SD)	
Copy **	34.9 (2.05)	23.6 (9.43)	27.7 (6.95)	†
IR**	22.3 (6.69)	5.0 (3.34)	10.6 (7.81)	††
DR**	21.7 (7.51)	1.9 (2.79)	8.2 (6.56)	†††
Strategy**	30.1 (3.52)	17.4 (8.58)	21.9 (7.44)	††††

** $p < .001$
† HC vs. AD ($p < .001$), HC vs. VaD ($p < .001$), AD vs. VaD ($p = .05$)
†† HC vs. AD ($p < .001$), HC vs. VaD ($p < .001$), AD vs. VaD ($p = .02$)
††† HC vs. AD ($p < .001$), HC vs. VaD ($p < .001$), AD vs. VaD ($p = .006$)
†††† HC vs. AD ($p < .001$), HC vs. VaD ($p < .001$), AD vs. VaD ($p = .03$)

4.3. Sex Differences in Healthy Control Group

As a second analysis, sex differences within the HC were evaluated. The demographic characteristics and BDI and MMSE scores are found in the Table 4.9. There were no significant differences in age, education, BDI scores or MMSE scores between males and females [Age: $F(1, 29) = 3.37$, $p = .07$, Education: $F(1, 29) = 3.43$, $p = .06$, BDI: $F(1, 29) = 1.99$, $p = .17$, MMSE: $F(1, 29) = .38$, $p = .54$].

Table 4.9. Demographic characteristics of Healthy Control (BDI and MMSE)

	Males (n=15) Mean (SD)	Females (n=15) Mean (SD)
Age	73.7 (4.03)	76.6 (4.70)
Education	13.5 (2.23)	11.8 (2.68)
BDI	5.7 (4.67)	8.1 (4.43)
MMSE	29.4 (.74)	29.2 (1.01)

Table 4.10 presents the means and SDs of all tests. On the Digit Span Backward Task, no sex differences were found in any trials [3-span Any: $F(1, 29) = 3.38$, $p = .06$, 3-span Serial: $F(1, 29) = .70$, $p = .40$, 4-span Any: $F(1, 29) = 1.09$, $p = .31$, 4-span Serial: $F(1, 29) = .15$, $p = .70$, 5-span Any: $F(1, 29) = .59$, $p = .45$, 5-span Serial: $F(1, 29) = 1.62$, $p = .21$]. On the letter and semantic fluency tests, there were no sex differences [Letter Fluency: $F(1, 29) = .25$, $p = .62$, Animal Fluency: $F(1, 29) = 2.46$, $p = .13$]. No sex differences were found in digit symbol or symbol copy tests [Digit symbol: $F(1, 29) = .001$, $p = .98$, Symbol copy: $F(1, 29) = .31$, $p = .58$]. The clock drawing or JOLO also did not demonstrate sex differences [Clock Command: $F(1, 29) = .28$, $p = .60$, Clock Copy (impossible to analyze because all participants scored "0"), JOLO: $F(1, 29) = .37$, $p = .55$]. Finally, on the Immediate Recall and Delayed Recall of the ROCFT, there were sex differences [IR: $F(1, 29) = 4.57$, $p = .04$, DR: $F(1, 29) = 3.99$, $p = .05$]. Males recalled the complex figure better than females; however, no sex difference was found in Strategy [$F(1, 29) = 1.58$, $p = .22$]. Males and females in HC group used a similar approach to copy the figure.

Table 4.10. Means and Standard Deviations of All Tests

		Males (n=15) Mean (SD)	Females (n=15) Mean (SD)
DBT	3-span (Any)	100 (0)	98.3 (3.09)
	3-span (Serial)	95.3 (5.16)	92.7 (11.20)
	4-span (Any)	96.1 (5.73)	93.7 (6.83)
	4-span (Serial)	83.1 (17.47)	80.6 (18.70)
	5-span (Any)	90.8 (8.84)	88.5 (7.82)
	5-span (Serial)	73.9 (17.52)	66.3 (15.12)
Letter Fluency		26.8 (6.57)	28.0 (6.64)
Semantic Fluency		19.5 (3.98)	17.3 (3.94)
Digit Symbol		61.0 (13.43)	61.1 (14.12)
Digit Copy		115.7 (20.71)	110.7 (27.97)
Clock	Command	.6 (.63)	.47 (.74)
	Copy	0 (0)	0 (0)
JOLO		98.9 (2.81)	97.8 (6.64)
PVLT	Total	35.9 (5.11)	35.7 (3.41)
	SDFR	6.3 (2.35)	6.7 (1.75)
	SDCR	7.5 (1.30)	7.8 (1.05)
	LDFR	7.4 (1.84)	7.3 (1.22)
	LDCR	7.8 (1.37)	7.8 (1.08)
	Recognition	95.7 (3.99)	96.1 (6.01)
Rey	*IR (p = .04)	24.8 (6.77)	19.8 (5.83)
	**DR (p = .05)	24.3 (8.00)	19.2 (6.23)
	Strategy	30.9 (3.02)	29.3 (3.90)

CHAPTER 5. DISCUSSION

This study aimed to 1) identify appropriate neuropsychological tests to differentiate Japanese AD and VaD patients, and to 2) examine how Japanese AD and VaD patients perform on those tests. In order to achieve these goals, a total of nine tests and 23 variables were compared. All tests demonstrated that they can be used as screening tools to detect whether or not the individual suffers from dementia because all tests have shown significant differences between healthy controls and dementia groups. Each cognitive domain will be discussed below.

5.1.1. Executive Control

It was hypothesized that VaD patients would perform worse on executive control ability tasks than AD patients; however, the Digit Span Backward Task was unable to differentiate between AD and VaD. Many western studies have shown that VaD patients were more dysexecutive and performed more poorly on executive functioning tests than AD patients, including letter fluency, Clock drawing, and Similarities on the WAIS-III (Garrett et al., 2007; Lamar, Price, Davis, Kaplan, & Libon, 2002; Lamar, Swenson, Kaplan, & Libon, 2004; Looi & Sachdev, 1999). The Digit Span Backward Task was also considered as a helpful tool to differentiate between AD and VaD (Oosterman & Scherder, 2006); however, this study did not demonstrate a similar finding. In addition to the Digit Span Backward Task, letter fluency and Clock Drawing command trial were thought to be measures for executive functioning but neither of the tests was able to distinguish between Japanese AD and VaD. It is possible that the Japanese elders with VaD have less executive functioning problems. Based on Tei and colleagues' study, the Japanese VaD patients were significantly more dysexecutive than the Japanese AD patients (Tei et al., 1997); however, it is important to note that Tei and colleagues used the Wisconsin Card Sorting Test (WCST), and their VaD patients made significantly more perseveration errors on the WCST than AD patients. The WCST is widely used in both western and eastern studies to assess executive functions; however, interestingly, the WCST has not often used for differentiation between AD and VaD in both western and eastern cultures (Looi & Sachdev, 1999). As different tests were used in present study, we cannot directly compare our study to Tei's study, but why did the current study not find similar results?

First, it is possible that the Japanese VaD patients may not have more executive problems than the AD patients. In fact, although Tei and colleagues did not necessarily consider letter fluency test as an executive functioning task, AD and VaD groups in Tei's study performed similarly on their letter fluency task (Tei et al., 1997), which is consistent with findings in this study. It is important to note that "executive functioning" can mean various cognitive abilities, such as planning, problem solving, mental flexibility, initiating and stopping actions, monitoring and changing behavior, and so forth. The Japanese VaD patients might not have significant impairment in working memory, which was measured in this study, but it does not necessarily mean that the Japanese VaD patients do not have deficits in other areas of executive functioning.

Second, Ishii and colleagues addressed that clinical symptoms of subcortical infarcts could be accounted for by frontal dysfunctions, and they demonstrated that the majority of infarctions were located in more anterior regions based on autopsy data (Ishi, Nishiahara & Imamura, 1986). It has been demonstrated that individuals with higher leukoaraiosis or white matter change performed worse on the Digit Span Backward Task and the letter fluency test (Lamar et al., 2007). The VaD patients in the present study were selected based on the brain CT-scans or MRI films; however, their level of leukoaraiosis, or the volume of white matter change, was not measured. Therefore, it is unclear if the VaD patients had significantly higher leukoaraiosis than the AD patients, or if their white matter abnormalities were in the anterior part of the brain. Additionally, previous studies pointed out the heterogeneity of vascular dementia (Hachinski et al., 2006). It is true that advanced technologies and newer techniques, such as a measure of leukoaraiosis, allow us to indentify the characteristics of VaD more precisely (Libon, Price, Davis-Garrett, & Giovannetti, 2004; Olsson, Brun & Englund, 1996). Even though VaD patients generally show executive functional problems, it may depend on where in the brain the white matter changes are seen. It is possible that the VaD patients in this study might not have white matter lesions in the anterior part of their brains.

Third, as we discussed above, the Digit Span Backward Task is a tool to primarily measure working memory, which is considered to be a part of executive functioning. The test requires manipulating numbers while keeping the numbers in mind. According to the meta-analysis study, 66% of the studies that attempted to differentiate between AD and VaD by using working memory tests demonstrated that VaD performed worse than AD (Looi & Sachdev, 1999). This means that 34% of studies conducted in western cultures did not find a significant difference between AD and VaD. If Japanese VaD patients actually have fewer executive control problems than American VaD patients, it is not surprising that no significant difference was observed in this study. It would be interesting if Japanese VaD and American VaD patients' performances on the Digit Span

Backward Task were to be compared because there is no study that has done the cross-cultural comparison.

5.1.2. Information Processing Speed

As we hypothesized, VaD and AD patients performed similarly on tasks of information processing speed, which is consistent with Tei et al.'s study (Tei et al., 1997). The Digit Symbol (DS) test is thought to be a good test to detect dementias because patients with dementias show declines on this test even in early stages of the diseases (Strandt & Hill, 1989: Lezak, 2004). The DS test was able to differentiate between healthy controls and dementia groups in this study as well. The Symbol Copy (SC) test also showed a significant difference between healthy control and dementia groups. A western study demonstrated that the Symbol Copy test is useful to distinguish between AD and VaD as VaD patients do not improve their performance on the SC from the DS test due to bradykinesia (slow movement; Sakamoto et al., 2007). However, the current study did not demonstrate a similar outcome. DS and SC tests use symbols, which are similar to the Kanji characters; therefore, it was expected that Japanese AD and VaD patients would show no difference. The extensive training in written language as well as the mixed way of writing and reading from both right to left and left to right in Japanese might have prevented the VaD patients from significantly slowing down as compared to the AD patients on both DS and SC tests.

One of other possible explanations could be that DS and SC tests are sensitive tests to detect dementias but not to differentiate between AD and VaD. A meta-analysis study indicated that the majority of studies that used the DS test did not differentiate between AD and VaD (Looi & Sachdev, 1999). The uniqueness of the present study was to include both DS and SC tests since one previous study has shown that a within group analysis comparing DS and SC was able to differentiate between AD and VaD among American patients (Sakamoto et al., 2007). Sakamoto and colleagues did not compare the raw scores of DS and SC tests, rather, they compared the slopes; how AD and VaD patients improve their speed from the DS to the SC test. It appeared that the VaD patients drew more symbols than the AD patients on the DS trial; however, the AD patients copied more symbols on the DC trial. In other words, there seemed to be a trend that the AD patients improved their speed whereas the VaD patients did not. Different types of analysis might be able to show the difference between AD and VaD among the Japanese elders. Additionally, it appears that replication will be needed to investigate whether the DS and SC tests are sensitive to differentiate between AD and VaD in both Japanese and American populations.

5.1.3. Visuospatial Construction

Although it was hypothesized that VaD patients would perform worse on visuospatial tasks than AD patients due to their perseverative errors, AD patients actually performed worse than the VaD patients. Because the Clock Drawing test can be considered as an executive functioning test since it involves spatial planning, it was thought that VaD patients would perform worse than AD patients; however, no significant difference was found in AD and VaD patients' performance. Micrographia was witnessed in four patients in the VaD group; however, perseveration was not found. Moreover, AD patients performed worse than the VaD patients on both simple (JOLO) and complex spatial/constructional (ROCFT) tests. It is still debatable whether AD and VaD patients perform similarly or differently as western studies demonstrated mixed results (Looi & Sachdev, 1999). According to a meta-analysis study, 81% of studies showed no differences in visuospatial constructional abilities between AD and VaD (Looi & Sachdev, 1999). Tei et al.'s study also failed to differentiate between AD and VaD by using ROCFT (Tei et al., 1997). However, the present study was able to show that AD patients performed worse than VaD patients on both ROCFT and JOLO.

First, it could be possible that vigorous visual training in Kanji education might prevent differentiating even between HC and dementia groups. However, all visuospatial tests showed significant differences between HC and dementia groups. Based on the Copy trial and Strategy of ROCFT, when participants were asked to copy the complex figure, AD patients appeared to plan out poorly and to use a fragmented and disorganized approach. As a result, they inaccurately drew the figure even though it was presented in front of them while they were coping. The findings indicated that pathology of AD appears to impact Japanese elders' spatial ability. The visuospatial/ constructional abilities are generally governed by non-dominant hemisphere regardless of different ethnicities/ races; however, Asians appear to use more of the dorsal stream while Caucasians appear to use more of the ventral stream to assess spatial locations (Grön, Shul, Bretschneider, Wunderlich, & Piepe, 2003). Given that this study has demonstrated that the AD group performed worse than the VaD group while the majority of previous studies failed to differentiate between AD and VaD, it is possible that disruption is likely to be occurring between the occipital lobe and sensory cortex, although no study shows that the amyloid plaques and neurofibrillary tangles are found more in dorsal stream.

In addition, a newer study has shown that large numbers of neurofibrillary tangles were found in cortical layers II, III, V and VI in Brodmann's area 37 in AD brains

(Thangavel, Sahu, Van Hoesen, & Zaheer, 2008). It is believed that Brodmann's area is involved in object naming and recognition memory (Thangavel, Sahu, Van Hoesen, & Zaheer, 2008). Also, Brodmann’s area 37 is generally activated when Japanese read and write Kanji while Brodmann’s area 39 is associated with phonological letters (i.e. Hirakana, Katakana, and Roman letters) (Uemura, 2006). Thus, once AD starts damaging temporal cortex in the brain, including Brodmann’s area 37, the Japanese elders may lose their cognitive strength obtained through an intensive training in Kanji education. It is exciting that visuospatial constructional tests can be used differentiate between AD and VaD as the present study has demonstrated.

Interestingly, VaD group’s strategy score (21.9) is very similar to what has been witnessed in young healthy Japanese-American females (21.5) and healthy American females (20.4) (Sakamoto, 2006). This indicated that even though the Japanese VaD patients’ memory might suffer as compared to the Japanese healthy elders, the VaD patients were at least attempting to use a good strategy. It is possible that their Kanji training crystallized their visuospatial constructional ability in comparison to what is seen in western-educated groups.

5.1.4. Language/ Semantic Knowledge

Both letter and semantic fluency tests were able to detect dementias although they were unable to distinguish between AD and VaD. We expected that AD group performed worse on the Animal Fluency task due to impairment in semantic knowledge; however, AD and VaD patients performed similarly. The amyloid plaques are found in large numbers in the limbic and associative cortices of AD patients and the neurofibrillary tangles affect large regions of brain, especially the entorhinal cortex, hippocampus, parahippocampal gyrus and amygdale (Eriksen & Janus, 2007). Because semantic knowledge is mainly controlled in medial temporal lobes, it is reported that impairments in semantic knowledge are often witnessed even in the early stage of AD (Saffran & Schwartz, 1994). Although this study failed to show the difference in the semantic fluency, it is considered that there was a trend that AD patients would perform worse than VaD patients. It is possible that if we had a larger sample size, the difference between AD and VaD could have been merged. The semantic fluency test may not be as sensitive as other tests, however, this study has demonstrated the possibility of differentiating between Japanese AD and VaD.

5.1.5. Learning and Memory

It was hypothesized that the AD patients would perform worse on delayed recall and recognition trials for both verbal and non-verbal memory tasks than VaD patients, and this hypothesis was supported. On the verbal learning test, PVLT-J, the AD and VaD did not show different performances on Total, SDFR, SFCR or LDFR; however, VaD patients outperformed AD patients on LDCR and recognition trials. These results suggested that the VaD group was able to benefit from cues. In other words, it seems that the Japanese VaD patients have retrieval problems, while the Japanese AD patients have encoding problems. These findings are consistent with western studies (Price, Garrett, Libon, Swenson, Penney, Jefferson, et al., 2004; Lamar et al., 2007; Libon et al., 1996; Looi & Sachdev, 1999). The present study was able to demonstrate a great possibility of the PVLT-J to differentiate between AD and VaD even in early stage of diseases.

On the spatial memory test, ROCFT, even immediately after copying the complex figure, AD patients were not able to recall as much as VaD patients did. Twenty minutes after the first exposure to the figure, AD group recalled the figure more poorly than VaD group. Three AD patients could not remember the fact that they copied the figure 20 minutes earlier. Although Tei et al. (1997) found a difference only on the Delayed Recall (DR) trial, this study successfully showed a significant difference between AD and VaD even on the IR. When it was more closely looked at how AD and VaD patients approached the ROCFT, strategy scores demonstrated that the VaD patients consistently used a more continuous and organized way to draw the figure. The different approach might have led to the different results in spatial memory. In younger populations, native Japanese used a more holistic approach than Japanese Americans and Americans (Sakamoto, 2006). Additionally, the native Japanese recalled figure better than the Japanese Americans and the Americans (Sakamoto, 2006). It seems that Japanese individuals see objects as a whole rather than as details. The Japanese participants' unique approach appears to lead to a better performance on spatial memory. As mentioned above, at the time of copying, the AD patients used more fragmented and disorganized approach than did VaD patients. This disorganized approach did not appear to help AD patients maintain the spatial information even immediately after the copy condition. It is already shown that AD patients demonstrated impairments in copying. It is possible that impairments in spatial orientation and planning might contribute to poor performance on both IR and DR trials in AD group.

Second, as described earlier, the amyloid plaques and neurofibrillary tangles are found in large numbers in the limbic and associative cortices, especially the entorhinal cortex, hippocampus, parahippocampal gyrus and amygdale (Eriksen & Janus, 2007). It is simply possible that the Japanese AD patients' brains are affected by plaques and tangles in the medial temporal cortex. As a result, they performed significantly more poorly than the VaD patients. Thus, verbal and non-verbal memory tests demonstrated a strong indication that they can be a great tool to distinguish between AD and VaD in Japanese population.

5.2. Sex Difference in Japanese Elders

As a second analysis, sex differences in healthy control were evaluated. The majority of the tests were not able to show sex differences, which were overall inconsistent with western studies (Amponsah, 1997; Amponsah & Krekling 2000; Feingold, 1994; Orsini, Schiappa & Grossi, 1981; Orsini, Simonetta & Marmorato, 2004; Silverman, Phillips & Silverman, 1996); however, the Immediate Recall (IR) and Delayed Recall (DR) trials demonstrated that males recalled the Rey complex figure better than females. The strategy of the ROCFT indicated that the males and females used a similar approach to copy the figure. When younger native Japanese men and women were compared to see whether those two groups would show sex differences on the ROCFT, they did not demonstrate sex differences (Sakamoto, 2006). On the other hand, young Japanese Americans and Americans showed sex differences, and men in those two groups obtained significantly better scores than women on Strategy. Regardless of age differences, individuals with Kanji education demonstrated no sex differences on Strategy while male participants *favorably* performed better on memory tasks of ROCFT than female participants. It is likely that the intensive training in written language yield a similar approach in copying Kanji-like figure among Japanese elders. This study was able to show the same pattern whether young or old Kanji learners.

5.3. Summary

The present study was the first project which attempted to assess what neuropsychological tests could be used for differentiating between the Japanese AD and VaD, and how the Japanese AD and VaD patients would perform on those tests. Overall, this study demonstrated that all tests were able to detect dementias and to differentiate healthy control from dementia groups. In terms of distinguishing between AD and VaD, the present study indicated that verbal and non-verbal memory tests and visuospatial constructional tests can be great assets to differentiate two different types of dementia. AD patients performed more poorly on those tasks than VaD patients. The semantic fluency also showed a trend that it can be a useful tool. It was thought that the AD pathology might affect the Japanese elders the same way it affects the American elders, and this study supported this hypothesis. On the other hand, none of the executive functioning tests were able to differentiate VaD from AD even though it was hypothesized that VaD patients would be more dysexecutive than AD patients as western studies have demonstrated. It is possible that Japanese VaD patients are actually not so dysexecutive as compared to American VaD patients, or the Digit Span Backward Task was simply not sensitive enough to detect VaD patients' deficit in executive functioning. As it was expected, the tests for information processing speed were not sensitive enough to differentiate VaD from AD, and it can be thought that the extensive training in Kanji education and the mixed way of reading and writing might have prevented VaD patients to significantly slow down on SC test as compared to AD patients. Again, this is the first study attempting to differentiate Japanese AD and VaD by using western neuropsychological tests. This study should be replicated to see if the findings are valid.

In terms of sex differences among healthy Japanese elders, the ROCFT demonstrated that the Japanese men outperformed Japanese women on recall trials, which is consistent with western studies; however, no sex difference was found on Strategy. This unique finding is actually consistent with the outcome of Sakamoto's study, which compared young Japanese men and women's performances on ROCFT (Sakamoto, 2006). The current study indicated that the individuals with Kanji education are likely to use a similar approach when they copy the Kanji-like figure because of the way they learned 1050 Kanji characters in written language; however, like western studies have shown, spatial memory tasks appear to be a male favoring task.

In summary, the primary goals of the present study was to evaluate what neuropsychological tests would be sensitive to differentiate between Japanese AD and VaD and to examine how those two groups perform similarly or differently on the tests. There was only one study that explored the same topic but used different tests. Moreover, the previous study used different tests and failed to differentiate between AD and VaD in most of cognitive domains. It has been already 12 years since the last study was done, and it was urgent to evaluate and to find out what tests can distinguish between Japanese AD and VaD as early diagnosis and intervention could reverse VaD. It was interesting to see how AD and VaD affect Japanese brains, and this study suggested that 1) AD appears to affect elders regardless of cultural differences, and 2) Japanese VaD patients seems to have less severe executive control impairment than American VaD patients.

It is unclear how similarly or differently Japanese brains function and organize information as compared to western brains because there are only a few research studies that tried to assess neuro-functional differences between westerners and easterners by using neuroimaging. As Gron et al. (2003) demonstrated, different parts of the brain were activated when Asians and Europeans were asked to remember object locations. Moreover, behavioral studies in sociology and anthropology suggested cultural differences in ways how individuals looked at pictures and how they relate to those pictures (Chui 1972; Nisbett & Masuda, 2006). It is believed that both genetic and cultural factors interplay and govern one's cognition; as a result, differences in cognitive functions are often observed cross-culturally. One of the main differences between Americans and Japanese is written language, and it is likely that vigorous visual training in Kanji education produced unique outcomes in this study.

Even though all Japanese participants had Kanji education and obtained similar scores on a Kanji screen test, AD patients' performance on Copy trial of ROCFT was worse than HC and VaD groups. AD patients demonstrated poor spatial planning and organization, and their poor spatial planning appeared to lead to impairment in recall trials. This outcome suggested that no matter how much intensive training individuals have in Kanji education, AD would affect their visuospatial/ constructional ability as well as spatial memory. As described above, Brodmann's area 37 seems associated with Kanji interpretation and a new study has found large volume of neurofibrillary tangles in Brodmann's area 37 in AD brains. Once AD starts damaging brains, it may not really matter what one's premorbid cognitive functioning was as AD patients showed significantly poor performance even on simple spatial tasks (JOLO). On the other hand, Kanji education appeared to prevent Japanese VaD patients from slowing down on tasks of information processing speed. Moreover, VaD patients unexpectedly did not show significant impairments in executive functioning. Again, it is possible that Japanese VaD patients might not have significant white matter change in their frontal lobe, or even if they do, the change might less impact on their function in executive control. Thus, it is important for clinicians to keep in mind that Japanese VaD patients may show less impairment in executive function when they are assessed for dementia evaluation.

5.4. Limitations and Future Directions

One of the difficulties was to accurately diagnose AD and VaD. In the U.S., measuring leukoaraiosis by using brain CT scan or MRI is a new technique for diagnosis of VaD; however, the application was unavailable in this study because Nanpu hospital did not have a particular computer that could digitize the CT scans. It cannot be excluded that VaD group might have a wide range in terms of white matter change within the group, and it might lead to heterogeneous performances. It is ideal to use objective technique, such as measuring leukoaraiosis, for more precise diagnosis.

Furthermore, it was challenging to recruit Japanese AD and VaD patients since inclusion and exclusion criteria were stringent in order to have “pure” AD and VaD groups as much as possible. It took a longer time to evaluate possible participants, contact them, and administer the tests than it was expected. In addition, Japanese society is more of a family-based culture than American society; therefore, it was important to obtain permission from patients’ family members. Some families first showed resistance to have their loved ones participate in this research study because they felt that it would not directly help them. With the researcher’s additional explanation, the family members eventually allowed the researcher to test the patient. In spite of some families’ resistance, all patients who were contacted by the researcher participated in this study. Although it may take a long time and can be challenging, it is important to increase the number of subjects in future research as some results, such as semantic fluency and clock drawing, showed a trend for significant differences.

It is exciting that the Japanese version of PVLT developed specifically for this project has demonstrated its sensitivity to differentiate AD and VaD. Since there are no verbal learning memory tests officially used in Japan, some clinicians have already shown interest in testing out the PVLT-J for Japanese individuals. In order to evaluate its validity and reliability, it is crucial to administer PVLT-J to different populations in terms of age, sex, and educational levels. Developing norms among Japanese population will be an ultimate goal.

In addition to the PVLT-J, ROCFT, JOLO, and semantic fluency were found to be appropriate for distinguishing Japanese AD and VaD. Especially it was unique to include strategy analysis of ROCFT in the present study. There are other methods that evaluate one's spatial planning, such as Stern's strategy analysis (Stern et al., 1994). It would be interesting to see how Japanese AD and VaD patients perform differently measured by other strategy analyses. On the other hand, the Digit Span Backward Task, which is considered a sensitive test in American studies, failed to show significant differences. As Japanese VaD patients appeared less dysexecutive as compared to American AD patients, it may be interesting to add 6-span trials or to use different analyses, such as error analysis. Different types of analysis may yield to understand different types of errors and profiles that Japanese AD and VaD demonstrate.

The current study is the first attempt to assess the usability of neuropsychological tests developed in western countries for distinguishing dementia among the Japanese.

Because there is no previous study, it was challenging to conceptualize and integrate what findings are really speaking to. It is crucial to replicate this study with a larger sample size to re-evaluate neuropsychological profiles of Japanese AD and VaD. Additionally, as the present study utilized same tests that are used in western studies, it will be a next step to compare Japanese AD and VaD profiles to western AD and VaD profiles. This will yield a better understanding how AD and VaD impact elders' cognitive function across different cultures.

5.5. Conclusion

In conclusion, the present study was able to demonstrate the usefulness of verbal and spatial memory tests, visuospatial/ constructional tasks, and possibly a semantic fluency test. In terms of verbal memory, as many western studies have already shown, the Japanese AD patients have encoding problems while the Japanese VaD patients have retrieval problems. The Japanese VaD patients benefited from cues. It seems that the mechanism and pathology of Alzheimer's disease are similar regardless of ethnicity. Moreover, the PVLT-J was developed as a part of this project, and it showed its potential to be used to differentiate between Japanese AD and VaD. Since previously, there was no official Japanese version of a verbal learning memory test, it is exciting to present that PVLT-J will be an asset not only as a dementia screening test, but also as a sensitive test which can distinguish between Japanese AD and VaD. Japanese clinicians and researchers in dementia field have already started showing interest in using PVLT-J.

Regarding spatial memory, this study showed that the ROCFT is a powerful tool to differentiate between Japanese AD and VaD. It is more likely that Alzheimer's disease attacks the Japanese elders as the same way it damages American elders. Even though the Japanese use a unique written language that requires intensive spatial training, their advanced spatial ability does not seem reserved when Alzheimer's disease attacks their brains. As a result, we found that the ROCFT can be used for differentiation between Japanese AD and VaD.

Another key point of this study was that the Japanese VaD patients were not as dysexecutive as the American VaD patients. It is unclear whether the tests that we used in this study were not sensitive enough, or the Japanese VaD patients are actually less impaired in executive control. If the former is the case, it is important to develop new executive functioning tests that are sensitive enough to detect the Japanese VaD. It is also possible that the Digit Span Backward Task can be made more challenging, including providing more numbers of 5-span trials or adding 6-span trials. It may be interesting to see how the Japanese dementia patients perform on the 6-span trials. If Japanese VaD patients are simply not dysexecutive, then it should be considered to take out tests for executive functioning for differentiating between AD and VaD. However, it is important to keep in mind that the Tei et al.'s study was able to distinguish VaD from AD by using WCST. If other executive functioning aspects rather than working memory were examined, there might have been significant differences between AD and VaD. Except for Tei's study, the current study is the only one which attempted intensively to differentiate between Japanese AD and VaD by using western neuropsychological tests; therefore, it is crucial to replicate this study with a larger sample size.

It is exciting that the current study was able to identify sensitive and appropriate tests for differentiating different subtypes of dementia among Japanese elders. Early and precise diagnoses can lead to both a better treatment plan and prognosis because VaD is treatable. It is important to continue to explore what tests are usable for differentiating Japanese AD and VaD. Moreover, the continuous effort in dementia research of Japanese culture will help decrease patients' families' tremendous distress if early diagnosis and intervention can reverse or slow down the disease.

At last, it is important to emphasize that this study pointed out an importance of paying attention to variability in neuropsychological profiles across different ethnicities and races. Neuropsychologists should carefully select appropriate tests for an individual based on his/her cultures and attentively interpret test results because they may be either consistent or inconsistent with "typical" performances that are observed among the majority. The most crucial job for neuropsychologists to be a "diplomat" in order to build a bridge between brain and behaviors/cognition, and to speak out how they are interacting based on one's cultures, ethnicities, races, and genders.

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VITA

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