

Does Prior Traumatic Brain Injury Increase Cognitive Impairment in the Elderly?

by

Bonnice A. Motier
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We accept this thesis as conforming to the required standard

Dr. John Allyn Higenbottam, Supervisor (Department of Psychology)

Dr. Bram Goldwater, Supervisor (Department of Psychology)

Dr. Clay Holroyd, Internal Member (Department of Psychology)

Dr. Margaret Penning, Outside Examiner (Department of Sociology)

Dr. Elaine Gallagher, External Examiner (School of Nursing)

Supervisors: Dr. John A. Higenbottam (University of Victoria)

Dr. Bram Goldwater (University of Victoria)

Abstract

There is research which demonstrates that traumatic head injury (TBI) is associated with increased incidence of dementia as well as with greater cognitive impairment than is expected in normal aging. However, this literature remains equivocal; studies exploring head injury as a risk factor for dementia and Alzheimer's disease have yielded conflicting results. The present study examines morbidity, mortality, cognitive impairment and psychosocial issues in seniors with a history of head injury of sufficient severity to cause loss of consciousness. These results suggest that over time, a history of TBI is associated with some increased morbidity with age. Associations between TBI and changes in personality that may lead to impaired psychosocial functioning were also suggested by the findings of this study. Specifically, the results indicated traumatic brain injury may be associated with marital breakdown and social isolation. Additional results suggest that people who have sustained a TBI have an increased likelihood of living in a nursing home or chronic-care facility.

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Does Prior Traumatic Brain Injury Increase Cognitive Impairment in the Elderly?

Traumatic Brain Injury (TBI)

Background

Is traumatic brain injury (TBI) a risk factor for the later onset of dementia? Similarly, is a history of TBI associated with a greater likelihood of cognitive impairment than expected with aging in individuals who do not develop dementia? The present study explores the relationships among TBI, dementia, cognitive changes and psychosocial issues in samples of elderly Canadians. It is hypothesised that TBI is a risk factor for increased dementia, accelerated cognitive impairment and negative psychosocial sequelae. The relevant literature is summarised, followed by a description of the method, results and discussion of results for this study.

The present work contributes to our understanding of the relationships among traumatic brain injury, dementia and cognitive changes in seniors. Better understanding of these relationships may aid in the prevention, early detection, and treatment of dementia and it may increase our ability to identify the needs of those with previous injury.

Incidence and Prevalence of Traumatic Brain Injury (TBI)

The incidence of traumatic brain injury (TBI) in Canada is estimated at 120,000 new cases per year with a prevalence of 400 per 100,000 across groups (Rosenthal & Ricker, 2000). Head injury accounts for up to half of all deaths from trauma (Kraus, 1993).

While young adults (males in particular) are at highest risk for TBI, children and older adults make up the second and third most frequently injured age groups (Fields, 1997). It is

important to note that the increased incidence of TBI among children and young adults may have long-term implications that may be reflected in accumulated prevalence of TBI over time thus with age.

Diagnostic Criteria for TBI

Loss of consciousness (LOC) after a head injury, essentially identical to the older term *concussion*, is a commonly used indicator of the severity of TBI. The importance of LOC is based on early studies of biomechanical forces in TBI (Ommaya & Gennarelli, 1974; Gennarelli et al., 1982). Animal studies have shown that a greater degree of rotational acceleration is required to produce LOC than to produce other symptoms such as amnesia. In the case of mild TBI, loss of consciousness is a less precise predictor of severity or indication of outcome because even ‘mild TBI’ without LOC can result in cognitive and/or functional impairment (Lovell, Iverson, Collins, McKeag, & Maroon, 1999; Kay et al., 1993; Rimel, Giordani, Barth, Boll, & Jane, 1981). Further, the chances of sustaining an additional concussion increase with each injury and successive concussions are described as having an ‘exponential effect’ on functional and cognitive functioning (Rabadi & Jordan, 2001).

Most neuropathologists maintain that even a brief LOC in TBI is likely to reflect some degree of diffuse axonal injury (DAI) which is likely to be permanent (Guberman, 1994; Webb, Rose, Johnson & Attree, 1996). The Glasgow Coma Scale (GCS) is routinely used in acute care settings to help in triage of TBIs. The scale is based on the patient’s motor response, verbal response, and eye opening. Scores range from 3 to 15; a patient with a score below 8 is considered comatose or unresponsive to external stimuli. Those with GCS below 8 have a 50 percent or greater chance of sustaining permanent neurological injury. Scores

between 13 and 15 indicate mild TBI. Patients in this range may not experience LOC, but simply a period of confusion. Although the GCS has been demonstrated to predict mortality (GCS less than 8 predicts a greater than 50% likelihood of dying within one month), efficacy in prediction of functional outcome has been questioned (McCullagh, Oucherlony, Protzner, Blair & Feinstein, 2001; Zafonte et al., 1996). Further, although brain injury may range from mild to severe, people who experience a brain injury may appear fine physically and yet have sustained a brain injury that affects their ability to resume normal life. Finally, the severity of TBI may be of lesser predictive value once a person reaches old age (Rothweiler, Temkin & Dikmen, 1998).

Neuropathology of TBI

Effects of TBI include primary damage to brain tissue at the impact site from mechanical forces, and secondary effects from other mechanisms. The later include a release of neurotoxins, brain ischemia, delayed subdural hemorrhage, and cerebral edema. Guberman (1994) reported that early pathophysiological features of TBI include altered blood flow, altered brain metabolism, and neurochemical excitotoxicity. Excitotoxicity includes apoptotic cell death; that is, active suicide that cascades through the tissue resulting in a diffuse loss of cells extending beyond the site of injury (Rink et al., 1995). Neurons also die as a result of necrosis, which is characterized by passive swelling, and leads to membrane lysis and release of intracellular constituents that evoke an inflammatory reaction (Majno & Joris, 1995).

Most TBIs occur under conditions of rapid deceleration resulting in injuries to frontotemporal structures. However, the primary neuropathology of TBI is diffuse axonal

injury (Povlishock et al., 1986). Diffuse axonal injury (DAI) occurs as a result of contrecoup injuries and rotational shearing as the brain glides or rotates within the cranial cavity due to impact forces. Dura matter protrusions restrict the brain's movement and enhance these shearing stresses. DAI is presumed by some to have occurred whenever there is any loss of consciousness (Meythaler, Peduzzi, Eleftherious & Novak, 2001), so the outcome of TBI is dependent primarily on the amount and distribution of axonal damage. This notion came from a large primate study conducted by Gennarelli et al. (1982) which showed that the presence and extent of DAI correlated highly with four variables: lateral direction of acceleration, duration of coma, degree of neurological impairment and outcome from injury. In animal models, the mechanism of TBI is the same as for humans. Further, the mechanism is the same regardless of severity; there is simply more damage in severe cases (Gennarelli et al., 1982). Likewise, in human cases of mild TBI that have been examined postmortem, the pathology is the same as in the severe cases; there is simply less of it (Oppenheimer, 1968).

The primary distribution of DAI injury seems to be in parasagittal deep white matter spreading from cortex to brainstem (Gennarelli et al., 1982). This localization may account for deficits in memory, attention and executive functions that are common in even mildly impaired TBIs (Alexander, 1995). Bostrom & Helander (1986) reported that DAI lesions eventually become the sites of degenerative changes and scar tissue or simply little cavities. Ventricular enlargement, demonstrated by computerized tomography (CT) scans, was found in 72% of a series of patients with severe closed head injuries (Bigler et al., 1996). This comes from shrinkage of brain substance due to disintegration of severely damaged neuronal tissue.

Meythaler et al. (2001) reported that the undersurface of frontal lobes, prefrontal lobes, tips of the temporal lobes, and lips of the Sylvian fissure are particularly vulnerable sites in TBI. It has also long been speculated that hippocampal structures are particularly vulnerable to trauma because of the frequency with which memory disorders are seen in post-injury survivors. This vulnerability is likely due to both the structural fragility of hippocampi and their proximity to the foramen magnum. This placement becomes an issue in the context of acute severe TBI wherein hippocampal structures are damaged by generalized swelling and raised intracranial pressure. This phenomenon is of significance in that the hippocampal complex has been linked to encoding and recall of new information (Nadel & Moskovitch, 1998). Further, recent findings by Wirth, Yanike, Frank, Smith, Brown & Suzuki, (2003) suggest that the hippocampus may be involved in signalling even very well-learned information. Additionally, the combination of injury to frontal lobes and hippocampal structures is likely to affect working memory which most maintain is dependent upon interactions between the hippocampal structures and the frontal cortex. (McClelland, McNaughton & O'Reilly, 1995).

Neurobehavioural Sequelae Following TBI

Physical, behavioural, and mental changes in TBI depend on the areas of the brain that are injured. Cognitive sequelae include changes in memory, attention, and concentration, (National Institutes of Health Consensus Development Panel on Rehabilitation of Persons With Traumatic Brain Injury, 1999). Alexander (1995) also reported that memory and attention are typically affected in TBI survivors along with perception, and judgment. Dombovy & Olek (1996) reported that learning and information processing, communication,

and emotional control are also affected by TBI as is the spontaneous recall of new information, as well as sustaining, shifting and dividing attention (Lezak, 1995). The ability to think in an abstract manner may be reduced as well as the ability to integrate new information (Alexander, 1995). Applying new information or showing flexibility across changing situations is also frequently impaired. Although a broad range of cognitive deficits may occur following TBI, deficits in specific areas of memory and judgment seem to predominate (Levin, Grossman, Rose & Teasdale, 1979; Jennet, 1996). Survivors of TBI usually maintain old memories but often lose the ability to record new memories. Meythaler et al. (2001) reported that the most common deficit in severe TBI is learning new information. In their study, 76% of severe TBI survivors showed these deficits. Curtiss, Vanderploeg, Spencer & Salazar (2001) reported that TBI survivors show specific deficits in encoding and retrieval of new memories.

Deficits in executive functions are also common in TBI (Cummings, 1993). Executive functions include the ability to plan, organize, monitor, and adjust behaviour in real time. Executive functions are closely related to attention and working memory (e.g., Barkley, 1996, Esslinger, 1996; Pennington, Bennetto, McAleer, & Roberts, 1996). Executive functions are fundamental to setting and attaining future goals, regulating affect, and controlling behaviour. These are problem-solving processes that are invoked when tasks are non-automatic and novel (Hayes, Gifford & Ruckstuhl, 1996). Executive functioning is directly involved in response inhibition and is associated with the frontal lobes. Decreased social awareness is also attributed to frontal lobe lesions; this can contribute to deficits in planning and modulation of behaviour. Other, social and emotional deficits have also been linked to damage to the specific areas of the prefrontal lobes (Cummings, 1993).

TBI: Changes in Personality and Impaired Psychosocial Function

Traumatic brain injury often results in emotional disturbance which interferes with employment, social relationships, and the enjoyment of life. A Canadian survey of 454 moderate and severe TBI survivors, with an average time of 13 years post injury, found that 90% of survivors had limitations or dissatisfaction with their social integration and relationships (Dawson & Chipman, 1995).

Prominent emotional changes after TBI include irritability, depression, nervousness, apathy and anger (Alexander, 1995). Emotional changes often occur, as well as decreased social awareness. These changes may be the result of damage to the lateral portions of the frontal lobes that can lead to inertia and indifference. Whereas, damage to the medial or orbitofrontal areas has a very different effect, depriving one of judgment and restraint; and opening the way to a non-stop stream of impulses and associations. The changes in personality in combination with persistent cognitive loss and other neuropsychological symptoms greatly impair the capacity of survivors to adapt after TBI and can place tremendous stress on social relationships.

Personality change and impaired psychosocial function have been noted in adult survivors at all levels of TBI severity (Spatt, Zebenhoizer & Oder, 1994; Hoofien, Gilboa, Vakil & Donovick, 2001) including mild TBI (Kay et al., 1993; Levin et al., 1979; Parker, 1996). Increased family strain and decreased psychosocial functioning have also been reported in older TBI survivors (Susman et al., 2002) who may be at even greater risk for the psychosocial impact of their injuries.

In cases of severe disablement after injury, spouses often become caretakers of their now dependent partners. Studies have highlighted the burden placed on family members and

close partners of individuals who have sustained traumatic brain injury (Gray, Shephard, & McKinlay, 1994). This burden of stress has been attributed to the neurobehavioural sequelae of the injuries. Wood & Yurdakul (1997) reported that 49% of TBI survivors had divorced or separated from their partners during a 5-8 year period following brain injury. Boswell, McErlean & Verdile (2002) also reported that survivors of TBI are less likely than people without TBI to remain with their partners. In the years following a TBI, the survivor's ability to maintain supportive familial relationships decreases. Although there is a tendency toward gradual improvement, many survivors are left with significant psychosocial and emotional sequelae that likely persist into old age.

Premorbid Personality and TBI

In addition to post-injury personality change, there is also evidence of an association between premorbid personality or premorbid functioning and TBI. Risk factors for TBI include substance abuse and psychiatric conditions associated with impulsive behaviours, such as bipolar disorder, cluster B personality disorders, and attention-deficit/ hyperactivity disorder (Sparadeo, Strauss & Barth, 1990). These pre-injury psychiatric conditions are associated with high-risk behaviours that can lead to TBI. Alcohol intoxication also frequently contributes to the occurrence of traumatic brain injury. The risk of head injury actually increases as a person's blood alcohol level increases. A Canadian study showed that more than 50% of TBIs involved alcohol intoxication, and 35% to 50% of patients arriving at Canadian emergency rooms with a traumatic brain injury had a history of abusing alcohol and other drugs. (Finnerty & Perron, 2006). Additional research results revealed that among trauma patients who had been binge drinking, the most common causes of head injuries were

assaults, falls and bicycling accidents (Health Canada, 2005). Further, a considerable proportion, that is, around two thirds, of adolescents and adults hospitalized for traumatic brain injuries have pre-injury substance use disorders (Corrigan, 1995). There is evidence that these disorders continue post injury. A remarkable number of studies have shown that among patients with the most severe brain injuries, alcohol or other drug consumption declines in the immediate post-injury period; however, people tend to return to pre-injury levels of use by two years post injury (Corrigan & Rust, 1995; Kreutzer & Witol, 1996; Corrigan & Smith-Knapp, 1998).

A large number of head injuries are preventable or in the least can be reduced by managing the risks. Traumatic brain injuries are often sustained by ‘risk takers’ or those who engage in behaviours that place them at greater risk for head injury (e.g. not wearing seatbelts or protective head gear, playing dangerous or contact sports, driving recklessly, operating equipment or driving while impaired, and substance use/abuse). Also, since the behavioural tendencies of the brain injury survivors continue after the injury has been sustained, the risks associated with an additional TBI are increased.

TBI is frequently complicated by psychiatric and psychological symptoms that are determined by a multitude of factors. These may include compromised mobility and balance, reduced capacity for judgment and behaviour modulation in addition to pre-existing tendencies, habits and behaviours. The interaction between neurobiologic changes and changes to the external social environment (i.e., relationships) may lead to psychosocial morbidity, even in the absence of profound neurologic or cognitive impairment.

TBI and Mortality

At this time, there is a lack of information regarding the relationship between persons aging with a history of TBI and the clinical course of cognitive decline leading to dementia and death. Mortality studies involving TBI survivors have consistently shown that older persons are at greatest risk of succumbing to their injuries during the immediate post-acute phase of recovery (Susman et al., 2002; Van der Sluis, Klasen, Eisma & Duis, 1996). Baguley, Slewa-Younam, Lazarus & Green (2000) monitored adult survivors of moderate to severe TBI for nine years post injury and reported that death rates among those who sustained traumatic brain injuries were higher than those of the general population. Additionally, Shavelle, Strauss, Whyte, Day & Yu (2001) examined mortality rates among traumatic brain injury survivors and reported significantly more deaths among TBI survivors who had been identified as disabled after their injury when compared to the mortality rates of nondisabled survivors. However, we do not know if a TBI survivor has persistent increased cognitive morbidity and mortality that extends into old age. Additionally, it is not known if the older TBI survivor continues to have high mortality after the acute medical and neurological symptoms have been resolved.

TBI and Cognitive Decline in Aging

There is very limited research exploring cognitive decline in aging TBI survivors. Current findings of cognitive and functional outcomes after TBI taken from younger adults may have limited application to older TBI populations. Further, many of the studies with older TBI survivors are cross-sectional in nature and simply compare the abilities of older people to those of younger people (e.g., Van der Sluis et al., 1996; Webb et al., 1996).

However, such cross-sectional studies, at best, offer a static picture of an elderly person (at a particular point in time) rather than revealing the clinical course and rate of cognitive decline as the person ages. Consequently, while the cross-sectional approach does address the issue of age *and* brain injury, it is an entirely different matter than the issue of aging *with* a brain injury; that can best be captured in a longitudinal approach.

Identifying the relationship between TBI and cognitive decline in older age has been complicated by attempts to separate the effects of ‘normal’ cognitive decline from the effects of a previous traumatic brain injury. In a review of outcome following TBI in elderly Canadians, Rapport & Feinstein (2000) concluded that methodological problems in the studies to date, in particular the failure to address premorbid functioning of TBI survivors account for equivocal findings on Alzheimer’s disease risk. Cross-sectional studies have revealed age-related differences in the morbidity associated with cognitive decline after TBI but the etiology of the decline has often been subject to the interpretation of the researchers. For example, some researchers have attributed lower memory scores obtained by TBI survivors to the normal decline associated with aging (Van der Sluis et al., 1996; Johnstone, Childers & Hoerner, 1998; Goldstein & Shelly, 1975). Additionally, Klein, Houx & Jolles (1996) explored early cognitive outcomes after TBI by comparing older and younger survivors. They reported significantly poorer performance by older survivors on tests of memory and executive function than either younger TBI or age-matched controls; nevertheless, they attributed the declined performance primarily to aging. Another limiting factor in the generalisability of the existing research in this area comes from studies that utilised very small sample sizes of persons over 65 (e.g. Goldstein & Shelly, 1975).

Alternate cross-sectional research has suggested that older TBI survivors do experience cognitive decline and but there are very few longitudinal studies of cognitive function completed with seniors psychosocial impairment beyond that expected in normal aging (Rothweiler et al., 1998), after TBI and even less that follow TBI survivors into old age. Thus, it is not really known if a history of TBI contributes to or accelerates the cognitive and memory impairment of an aging person beyond that of the original injury or beyond that expected given their age. This area of research is also complicated by difficulty in insulating sequelae associated with a TBI from the potential effects of premorbid dementia as well as our limited ability to estimate preinjury functioning in those with a history of TBI.

There have been a number of studies examining a variety of indicators of cognitive decline in small samples of elderly individuals with a history of TBI (Chandra, Philipose & Bell, 1987; Chandra, Kokmen, Schoenberg & Beard, 1989; Goldstein & Shelly, 1975; Klein, M., Houx, P. J. & Jolles, J., 1996; Van der Sluis, Klasen, Eisma & Duis, 1996). Few studies have examined indicators of cognitive decline or psychosocial impairment in a larger sample of elderly individuals with a history of TBI (Hoofien, Gilboa, Vakil & Donovan, 2001; Susman et al., 2002; Thomsen, 1992). Additionally, no studies were found that explored collateral reporting (by spouses or caregivers) of general decline in aging TBI survivors. Studies of cognitive function in older TBI populations have resulted in mixed and inconclusive findings and have been limited by their design and sample characteristics. Therefore, these issues severely limit our ability to generalize the findings to our understanding of the growing population of aging persons with TBI.

Aging Brain and Cognitive Changes

The Aging Brain

Advancing age is associated with a progressive loss of brain tissue, especially in the cerebral cortex (the grey matter). Fotenos, Snyder, Girton, Morris & Buckner (2005) reported finding that total brain weight and volume decrease by an average of 5-10 percent between the ages of 20 and 90. The same study suggested that nondemented individuals exhibit a slow rate of whole-brain volume atrophy from early in adulthood with white-matter loss beginning in middle age; in older adults, the onset of dementia of the Alzheimer type is associated with a markedly accelerated atrophy rate.

Structural studies of the aging brain indicate that the prefrontal cortices experience the highest degree of age-related atrophy (Raz et al., 1997; Raz, 2000). According to Ivy, MacLeod, Petit & Markus (1992), the primary area of neuronal atrophy during normal aging is both the frontal and prefrontal lobes. Research by DeCarli et al., (1995) has also suggested that temporal lobe volume does not decline in normal aging whereas posterior frontal lobe volume declines by approximately 1% per decade. Prefrontal regions have been found responsible for executive control for a wide variety of cognitive abilities including memory (Wagner, 1999) and attention (Banich et al., 2000)

In 1994, Breteler, van Swieten & Bots conducted a population-based study on the prevalence of white matter lesions in elderly persons as measured by magnetic resonance imaging (MRI). The results showed that there were increased lesions in elderly persons. In the same study, Breteler et al., (1994) reported that ventricular enlargement was associated with poorer scores on tests of global cognitive function whereas white matter lesions were associated with poor performance on tests of executive function.

Hippocampal atrophy is perhaps the best studied structural marker of aging related decline (Kesslak, Nalcoiglu & Cotman, 1991). Participants of what is known as the Nun Study, wherein 678 American members of the School Sisters of Notre Dame religious congregation who were 75 to 106 years of age agreed to psychological testing prior to death and to autopsy after death. Magnetic resonance imaging (MRI) from the Nun Study showed a strong correlation between decreased hippocampal volume and delayed verbal recall (Mortimer, Gosche, Riley, Markesbery & Snowden, 2004). Walhovd et al., (2004) also reported research that supports a critical role of cortical and hippocampal size in recall verbal memory tests. Their study assessed delayed recall after 5 minutes, 30 minutes, and a mean period of 11 weeks in seniors who were also autopsied after death.

The brain also looks different as it ages. Kesslak et al., (1991) reported that the grooves on the surface of the brain widen, while the swellings on the surface become smaller. Neurofibrillary tangles, which are decayed portions of the branch-like dendrites that extend from the neurons, also increase with age. Additionally, they reported that senile plaques, or abnormally hard clusters of damaged or dying neurons, form in the brain.

Although most will agree that some nerve cell loss occurs with age and that this loss is related to decreased cognitive function, this decline can reflect multiple causes related to aging. For example, decreased effectiveness of the blood-brain-barrier in aging brains has been suggested as a reason for cognitive decline in aging persons (Guberman, 1994). Additionally, it is suggested that as this barrier deteriorates and becomes permeated, the brain is at greater risk of exposure to β -amyloid. β -amyloid is associated with increased risk for Alzheimer's disease (Emmerling et al., 2000; Bondi, Salmon, Galasko, Thomas & Thal, 1999), particularly in cases of familial AD (Saunders et al., 1993). Cummings, Vinters, Cole

& Khachaturian (1998) maintain that all mutations known to cause Alzheimer's disease increase the production of beta amyloid peptide.

There are very large gaps in our understanding of the relationship between brain structures and cognitive decline associated with aging. At this time, the relation between neural loss as a result of aging and progressive loss of neurons due to the effect of disease is not known. A major obstacle has been the lack of agreement on what 'normal' neural loss is and a lack of agreement on what 'normal' cognitive loss is since there are large individual differences in degree, rate and pattern of cognitive change with age. These individual differences may be masked in the many studies that report group differences in dementia rates.

Cognitive processes are generally believed to be the result of integrated activity in networks of areas within the brain rather than activity of any area in isolation. Therefore, neuropathological processes associated with age may impose a reorganization of the functional connectivity between brain areas. As such, any loss would be attenuated by the redundancy of the neural system. However, while the brain can likely compensate for minor losses, extensive losses will probably translate into some loss of function and even dementia.

Cognitive Changes Associated with Aging

Cross-sectional research has shown that older adults can function cognitively within the range exhibited by 'normal' younger adults (Salthouse, 1991). Yet, clinical and research findings show decreased abilities in the following areas: fluency and naming, sustained concentration, problem-solving abilities, analysis of complex perception, constructional abilities, and general loss of processing resources (Forno & Kawas, 1995). Salthouse (1990)

also reported findings of slower processing speeds; reduced ability to divide, shift and sustain attention; and diminished memory in older adults when compared to those of younger age ranges.

The frontal lobe hypothesis of cognitive change associated with aging suggests that age-related cognitive decline reflects changes in executive processes and neural connections subserved by the frontal lobes (e.g., Albert & Kaplan, 1980; Banich et al., 2000; Stuss, Gallup & Alexander, 2001; Milham et al., 2002). Brain imaging studies in aging populations have supported this view. Attention has been linked to the frontal lobes. Study results have attributed decreases in the efficiency of working memory processing to possible declines in attentional control with age (Banich et al., 2000). Attention and working memory have been linked to the frontal lobes. For example, an fMRI study by Milham et al., (2002) comparing 60-75 year olds to 21-27 year olds, showed age-related decreases in structures thought to support attentional control (e.g. dorsolateral, prefrontal and parietal cortices). This research by Milham et al., suggests that with age there is decreased attentional control and subsequent decreased ability to inhibit the activity in the brain in processing task irrelevant information (2002). These findings are important because attention has also been linked to memory function (e.g. Wagner, 1999; Baddley, 1986).

The prefrontal lobes have also been implicated in the reduced ability to retrieve episodic information from the hippocampal system (Fernandes & Moscovitch, 2000). The interference of non relevant information during retrieval may help to explain the slower processing speeds of older participants when compared to those of younger participants.

Another related theory that has been put forth to explain the overall age-related change in cognitive functioning is the disconnection hypothesis. This view is supported by Adams

and his colleagues (Adams, Doyle, Graham, Lawrence & McLellan, 1985) who maintain that cognitive decline results from a change in the hardware of the neural network due to broken linkages. The rationale is that the greater the number of broken links, the longer the processing time. Therefore, any injury resulting in the death of neurons causes breaks and requires signals to find another route, thus increasing the amount of time needed and the potential for lost information. In keeping with this view, normal cognitive aging may be largely the result of a reduced supply of undamaged cells. However, despite fairly consistent group change in the cognitive abilities of older subjects, it is clear that these changes do not occur equally in all individuals (Maitland, Intrieri, Schaie & Willis, 2000). It is also important to note that this decline in cognitive functioning or memory is relative to previous ability.

Memory

Human memory is a remarkably complex cognitive function that has intrigued researchers for centuries. How we form memories, how they are retained and later retrieved are questions that have been investigated for decades. Considerable advances in neuroscience have been achieved due to animal lesion studies, the study of neuropsychological patients, and functional imaging studies. In particular, newer research methods like functional Magnetic Resonance Imaging (fMRI) have contributed to the progress in memory research.

Memory includes past experiences, knowledge and thoughts (Squire & Kandel, 2000). The construction of memories is generally believed to involve three steps: the acquisition of new information (encoding), the process by which this new information is stored or consolidated, and the process through which it is recalled (retrieval).

Memory, as the representation of an experience in the neocortical system, consists of a widely distributed pattern of neural activity. Information is encoded in patterns of the neural activity, which are weak and not yet persistent. Only later is it stored in more persistent molecular and structural formats by undergoing a series of neurophysiological processes (e.g., glutamate release, protein synthesis, neural growth and rearrangement) that render the memory representations progressively more stable. For many years, scientific thinking about memory was dominated by the assumption that memory is a unitary entity. However, this assumption has been challenged by converging evidence from psychology and neuroscience pointing toward multiple memory systems that can be dissociated from one another. Most who study memory divide it into at least two categories: short-term memory and long-term memory.

A review of the history of memory studies finds that the concept of short-term and long-term memory has evolved into a multicomponent system. A recent hypothesized model of memory based on that of Strauss, Sherman & Spreen (2006) is shown in Figure 1. In general, short-term memory refers to the holding of information in the conscious awareness for a short period of time. Long-term memory refers to material which is removed from conscious awareness but which is retrievable after longer periods of time.

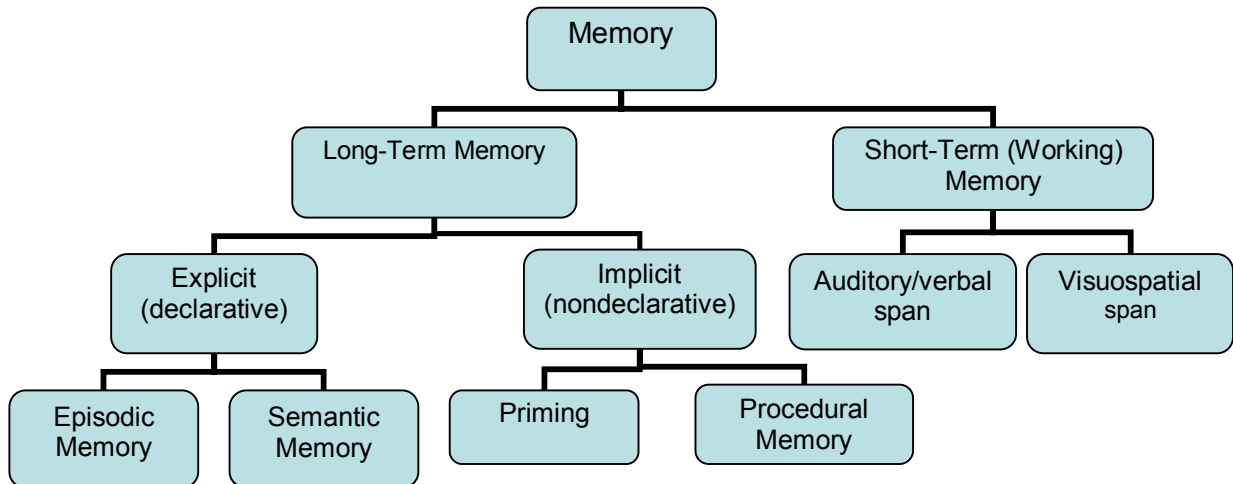


Figure 1. Hypothesised structure of memory. Based on Strauss, Sherman & Spreen, 2006 (with permission).

The relationship between short-term memory and working memory. Short-term (working) memory in the figure above refers to structures and processes used for temporarily storing and manipulating information. It has a very limited capacity in contrast to that of the long term. Although the figure suggests working memory and short-term memory are the same, the relationship between short-term memory and working memory is differently described by various theorists. It is generally acknowledged that the two concepts are distinct and that short-term memory storage is a function of working memory. Short-term memory is the immediate phase of the memory process by which a limited amount of stimuli that have been recognised and registered are stored briefly (roughly 15-30 seconds). Short-term memory is essential to the consolidation of information from working memory to long-term memory and utilises the hippocampal structures.

Working memory is ‘where the action is’, in that memory researchers consider working memory to be a specialised term referring to memory for information that is task relevant or associated with the task at hand. Working memory also refers to the somewhat

more complex attentional capacity for simultaneously storing and processing the information needed during cognitive performances. The hippocampus works with the prefrontal cortex during working memory. For example, functional Magnetic Resonance Imaging (fMRI) studies suggest the prefrontal cortex plays a pre-eminent role in the working memory processes of all sensory modalities (Cohen et al., 1997).

Comparisons among contemporary working memory models reveals: (1) consensus that the content of working memory includes not only task-relevant information, but also a process for inhibiting interference in the brain from nonrelevant or task-irrelevant information; (2) consensus that working memory consists of phonological and visuospatial components; (3) consensus that short-term memory storage is a function of working memory (Yuan, Steedle, Shavelson, Alonzo & Oppezzo, 2006). The main effects of aging have been shown to take place in long-term memory (e.g., Kazniak, Poon & Riege, 1986). However, although short-term memory is well preserved, working memory is strongly affected by aging.

The relationship between newly formed memories and long-term memories. The hippocampus and the neocortex are believed to play complementary roles in learning and memory (McClelland, McNaughton & O'Reilly, 1995). McClelland (1995) proposes that the hippocampus serves as both the initial cite of storage and also as teacher to the neocortex. According to the parallel distributed processing approach, (McClelland, 1995) all cognitive states are represented as patterns of activation that change through time. Cognition takes place via the interactions of a large number of simple but highly interconnected computational elements that are organised into groups or modules. According to McClelland's (1995) model, the neocortex uses a very gradual learning procedure that allows it to utilise the

structure in ensembles of inputs. The hippocampus is needed to complement the neocortex, providing a mechanism for rapid learning of the specific arbitrary aspects of particular items. In addition to the cortical system, there is rapid storage of traces of specific episodes within the hippocampus. A pattern of activation at the hippocampus with associated synaptic modifications takes place. Later when a retrieval cue is presented, this produces a partial reinstatement of the hippocampal input pattern. This is then completed by the hippocampus and then reinstated in the neocortex via return projections. As memories are formed or learning takes place there is an increase in the strength of excitatory (positive) and inhibitory (negative) connections among these modules. Then gradually through repeated reinstatement of the same trace, the cortex may receive enough trials with the same association to “learn it” in the neocortical connections. As time passes, cellular and molecular changes allow for the strengthening of direct connections between neocortical regions, enabling the memory of an event to be accessed independently of the hippocampus.

Recent experiments suggest that memory consolidation requires reactivation by the hippocampus. Wirth, Yanike, Frank, Smith, Brown & Suzuki, (2003) examined the neural correlates of associative memory formation by using electrodes to monitor the electrical activity of individual hippocampal neurons (called change cells) in the brains of monkeys performing an associative learning task. The changes in neural activity paralleled the animal’s behavioural learning curve indicating that these neurons are involved in the initial formation of new associative memories. However, because the activity in many change cells continued after the animal learned the association, this suggests that these cells may participate in the eventual storage of the associations in long-term memory. These findings are exciting because they suggest that the hippocampus is involved in signalling even very

well-learned information. This may be a way that well-learned information is incorporated into our memories of everyday episodes or events.

Long-term memory. A catch-all phrase that refers to the rest of memory is long-term memory (also seen in Figure1). Long-term memory is the aspect of the memory process whereby information that has been registered and encoded is gradually stored permanently for future retrieval. It refers equally to events or facts learned minutes ago as well as things that have been learned as a child. As shown in Figure 1, theoretical components within long-term memory include implicit memory which is characterized by a lack of conscious awareness in the act of recollection. A component of implicit memory is procedural memory which allows us to learn new skills and acquire habits, whereas the other component, priming, refers to facilitated memory performance as a result of prior exposure.

Explicit memory as illustrated in Figure 1, is also a component of long-term memory. It involves conscious recollection in order to recall something. Explicit is sometimes referred to as declarative memory and is so called because it refers to memories that can be consciously discussed, or declared. It is contrasted with procedural memory, which applies to skills. Explicit memory is subject to forgetting, but frequently-accessed memories can last indefinitely.

Explicit memory has been divided up into episodic and semantic memory (Tulving, 1983). Episodic memories are those that have a time stamp on them. That is, they are specific episodes from an individual's life that are embedded in a temporal context. This includes both memory for significant life events and memory for common daily activities. Episodic memory is sometimes referred to as autobiographical memory. Ordinary memory tests of free recall, cued recall and recognition typically involve this type of memory. Semantic memory on the

other hand involves information that has lost its time reference. Thus, a semantic memory contains conceptual and factual knowledge, but the individual has forgotten where the information came from.

Neurophysiological correlates of memory function. Several brain regions have been associated with memory (Rolls, 2000): One memory system is involved in stimulus-reinforcer associations in which the reinforcing value of a previously neutral, e.g. visual or auditory, stimulus is learned because of its association with the primary reinforcer. This system is believed dependent on the orbitofrontal cortex and the amygdala. A second system in the temporal cortical visual areas is involved in learning invariant representations of objects. Third, brain systems in the frontal and temporal cortices have been implicated in short-term memory. Fourth, the medial temporal lobe (MTL), more specifically the hippocampus is thought to be involved in declarative memory (Tulving & Schacter, 1990).

However, the functional role of the hippocampus is a subject of controversy. Cohen and colleagues (Cohen et al, 1999) reviewed the literature on functional imaging studies of the hippocampal system and concluded that currently five different accounts of hippocampal function are prevalent. The five accounts are: novelty, retrieval success, explicit (declarative) vs. implicit (nondeclarative) memory, spatial (cognitive) mapping and relational memory processing.

One strong line of evidence which supports the hypotheses that the hippocampus is involved in declarative memory comes from amnesic patients. Human amnesia impairs the ability to acquire information about facts and events (declarative memory) but spares the capacity for skill learning, certain kinds of conditioning, and habit learning, as well as the phenomenon of priming (compare with Figure 1). Impairments in episodic memory have also been associated with lesions to the hippocampal system (Cohen & Squire, 1980). More recently, studies suggest that the right hippocampus is involved in the encoding of complex

abstract stimuli and scenes, whereas the left hippocampus is involved in the encoding of verbal stimuli (Constable et al., 2000).

The hippocampus is part of the medial temporal lobe (MTL) and can be divided into three parts: the hippocampal head (anterior segment), body (middle segment), and tail (posterior segment). It is bilaminar, consisting of the Cornu Ammonis (Amons horn or Hippocampus proper) and the Gyrus Dentatus (or Fascia Dentata), which are rolled up one inside the other. In general, the term hippocampus applies to the Cornu Ammonis with its four subfields CA1, CA2, CA3, CA4 and the Dentate Gyrus, that encloses the CA4 region.

Several case studies of neuropsychological patients with damage to the hippocampus have been reported during the last 100 years. The findings of all the patients reported so far lead to the following conclusions: Damage to the hippocampus by injury or neurodegenerative disorder (e.g. Alzheimer's disease) produces anterograde amnesia, a loss of memory occurring after the injury which caused the amnesia, as opposed to retrograde amnesia, which refers to the amnesia of all events prior to the injury.

Bilateral damage limited to the CA1 region of the hippocampal formation is sufficient to produce moderately severe anterograde memory impairment. Bilateral damage beyond the CA1 region, but still limited to the hippocampal formation, can produce more severe anterograde amnesia. Bilateral damage limited to the hippocampal formation can produce extensive, temporally graded retrograde amnesia covering >15 years (Zola-Morgan et al., 1995).

The term hippocampal region is different from the term hippocampal system. Whereas the term hippocampal system refers to the hippocampus and related medial temporal lobe structures (Cohen et al., 1999), the hippocampal region is a functional unit composed of the

entorhinal area, the Gyrus Dentatus, the Cornu Ammonis and the subiculum (Duvernoy, 1998). Adjacent cortical areas the entorhinal, perirhinal, and parahippocampal cortices – seem to play a crucial role in memory as well, which is indicated by human amnesia studies (e.g. see Eichenbaum et al., 1994; Zola-Morgan, Squire & Ramus, 1995). They are referred to as the parahippocampal region (Eichenbaum et al, 1994). Although animal lesion studies, as well as neuropsychological case studies and human memory studies with fMRI and PET consistently suggest that the hippocampus and adjacent structures play a role in memory, it still remains unclear which structures in the MTL are important for declarative memory and what their specific functions are.

Although memory is inherently intertwined with all other aspects of cognition, researchers have a tendency to discuss attention and memory in isolation from one another. Memory is heavily influenced by the attention paid to the stimulus during processing. Advances in our understanding of cognitive neuroscience have made it clear that memory and attention are mutually dependent functions that share many of the same neural substrates (e.g. dorsolateral prefrontal cortex, see Baddley, 1986). Additionally, flexible cognitive control over our behaviour is recognised as a key part of human intelligence and has been called the top down excitatory biasing model of cognitive control (e.g. McClelland et al., 1995). In cognitive control models the prefrontal cortex is viewed as maintaining representations that guide control of tasks (Herd, Banich & O'Reilly, 2006).

Research from cognitive neuropsychology and neuroimaging has implications for the connection between the frontal lobes and episodic memory (Schacter, 1987; Tulving, 1983). In particular, the prefrontal cortex, in conjunction with its reciprocal connections with other cortical and subcortical structures (including the hippocampus), is believed key to episodic

memory (Wheeler, Stuss & Tulving, 1997). Squire (1987) associated frontal pathology with a loss of “personal familiarity and connectedness” to recent events. Neuroimaging and lesion studies have already yielded evidence that the prefrontal cortex plays an important role in episodic memory, above and beyond any role it has in semantic memory (Wheeler, Stuss & Tulving, 1997). In a series of articles on findings from positron emission tomography (PET) studies, Tulving, Kapur, Craik, Mosovitch & Houle (1984) linked the left prefrontal cortex with episodic encoding and the right prefrontal cortex with episodic retrieval.

Additionally, research by Banich has pointed to the importance of interhemispheric interaction in attention via the corpus callosum (1998). This structure was shown to aid in the gating of sensory information, thus allowing for parallel processing through a division of labour between the two hemispheres and insulating activity between the two sides of the brain. It is believed that this process allows for dynamic interactions between the hemispheres and other structures and modulation of the processing ability of the brain (Banich, 1998). Tremendous advances have been made in our understanding of memory function, neural connections and attention. However, the relationship between neural substrates and how they relate to all aspects of memory is extremely complex and at this time is not fully understood.

Memory Changes Associated with Aging

Whether memory does or does not decline with age is dependent upon which aspect of memory is examined as well as the type of memory task assessed. In general, those memory tasks that are complex, effortful, require speed and the learning of new information appear to become more difficult to achieve as we age (Salthouse, 1990). Significant decline has been

demonstrated in older participants on a variety of cognitive measures, including tests that tap their memory for what was seen and what was spoken; that is, memory that is typically referred to as visual and verbal memory (Arenberg, 1990; Hultsch, Hertzog, Small, McDonald-Miszczak & Dixon, 1992)

Longitudinal research by Schaie & Willis (1993) supports the notion that, of verbal or visual memory, verbal memory is the best maintained. However, Spreen & Strauss (1998) advise that both verbal and nonverbal components of memory should be evaluated when testing diagnostic hypotheses. Additionally, they maintain that the efficiency of retrieval of both recently learned and remote information should be examined under both explicit and implicit conditions. The typical explicit memory task involves persons being shown a series of words or pictures and, later, being given a recall or recognition test that requires them to think back to produce the correct response.

A profound impairment in episodic memory is a hallmark of Alzheimer's disease that is seen very early in the pathogenesis and measures of episodic memory have been most predictive of AD (Mortimer, Borenstein, Gosche & Snowdon, 2005). A meta-analysis based on 47 studies of those with preclinical dementia showed significant impairment in cognitive domains including declarative episodic memory (story recall, word list learning) and global cognitive ability several years before clinical diagnosis of dementia (Backman, Jones, Berger, Laukkad & Small, 2005). In particular, this research group found that delayed recall-based assessments resulted in the largest effect sizes.

It is well known that age differences in memory abilities are larger in tests of free recall than for tests involving recognition or cued/assisted recall. Research reported by Wingfield & Kahana (2002) continues to support this view; specifically, when older adults are

tested, rates of decline in recall for unrelated word-lists can be five-times greater than for a matched group of young adults. Wheeler (2000) also reported that during free recall, older participants consistently forgot recently studied target words more rapidly than younger participants.

Dementia

Dementia: Diagnosis, Etiology, Prevalence and Clinical Course

Diagnosis. Aging increases the risk of cognitive dysfunction and dementia.

According to the Diagnostic and Statistical Manual of Psychiatric Disorders-IV-TR ([DSM-IV-TR] American Psychological Association, 2000), dementia is defined as an irreversible, abnormal decline in cognitive functions. Dementia involves impairment in memory and may involve language function, motor activities, visual recognition and executive function difficulties significant enough to impair social or occupational functioning. Hippocampal volume has also been shown to be a reliable index of Alzheimer neuropathology (Gosche, Mortimer, Smith, Markesbery & Snowden, 2002).

Etiology. Based on the DSM-IV-TR (APA, 2000), dementia is further defined by etiology: dementia of Alzheimer's type, vascular dementia, dementia due to other general medical conditions, substance-induced persisting dementia, dementia due to multiple etiologies, or delirium not otherwise specified.

Prevalence. The Canadian Study of Health and Aging Working Group (CHSA) reported that Alzheimer's disease represented 64% of all identified cases of dementia (1994). The prevalence estimates suggested that 8.0% of all Canadians aged 65 and over met the criteria for dementia. Further, the age standardised rate is 34.5% among those 85 and over

(CSHA, 2000). Further, according to the Canadian Alzheimer Society (2006), the estimated prevalence of Alzheimer's disease and related dementias in Canadians over 65 in 2006 is 453,000; women account for 298,000 cases and men, 137,000. If current prevalence rates remain constant, based on the figures collected in the CSHA study, the number of Canadians with dementia will rise to 592,000 by 2021. Using data from a 5-year cohort study of 10,263 seniors, the Canadian Study of Health and Aging Working Group estimated there are 60,150 new cases of dementia per year in Canada (2000). Estimates have been extrapolated from 1996 CSHA incidence data and project that new cases of dementia will reach 111,560 per year by 2011; of these, 67,680 will occur in women and 43,880 will occur in men (Canadian Alzheimer Society, 2006).

Clinical course. Mild slowing of cognitive processes is normal with aging and, by itself, does not suggest dementia. However, dementia is typically preceded by a state of mild cognitive impairment, or cognitive impairment without dementia (CIND) which may last for several years. CIND is characterized by the presence of a clinically observable cognitive impairment (usually isolated to memory), beyond what is expected from normal, age-related changes, but insufficient evidence to warrant a diagnosis of dementia (Tuokko & Frerichs, 2000). The classification of CIND, as described by Tuokko and Frerichs, requires objective evidence of cognitive impairment in one aspect of cognitive functioning, and is operationally defined as performance that is 1.5 standard deviations below age- and education-matched norms for the test used to assess that function (e.g., the Wechsler Memory Scale –III). It is also necessary for the individual to demonstrate no functional impairments and no dementia to qualify as CIND. In layman's terms, this means that there must be a measurable decline in memory and thinking abilities in a person that is below the scores of his or her peers with the

same education level, but there should be no decline in the person's ability to function in everyday life.

There are qualitative and quantitative differences in cognitive functioning between age-associated cognitive change, dementia and progressive disease. However, in their findings, Tuokko & Frerichs (2000) reported a significant proportion of persons with even mild cognitive impairment (CIND) involving memory progress to dementia over a 1- to 2-year interval and approximately 50% progress to dementia by 5 years. Generally, older adults with CIND or mild cognitive impairment, especially those with a variety known as amnesic (memory-related) mild cognitive impairment, are thought to have a higher risk of progressing to clinical Alzheimer's disease. This preclinical impairment is not isolated to AD, however. There is emerging evidence of a preclinical period with cognitive deficits in other disorders of dementia, such as vascular, frontotemporal and Huntington's (Backman et al., 2005). Yet little is known about how mild cognitive impairment or CIND affects the physical structures of the brain.

A primary early feature of dementia is memory impairment. Tierney and colleagues (1996) found that of the 123 elderly patients referred to them by the patient's family physician, 23.6% had memory problems severe enough to interfere with daily functioning. It is significant that these same individuals were also diagnosed with probable Alzheimer's disease within the 2-year follow up period.

Neuropharmacologic Treatment of Dementia

The strength of the relationship between the memory impairment associated with dementia and the hippocampal structures is also evident in the neuropharmacologic treatments for dementia developed over the last 25 years. Animal studies have shown that damage cholinergic input to the neocortex or hippocampus from the basal forebrain (e.g., nucleus basalis magnocellularis and medial septum/diagonal band) disrupt performance of the same memory tasks that are impaired with cholinergic blockade (reviewed in Decker & McGaugh, 1991).

Since the 1980's it has been generally maintained that Alzheimer disease (AD) and geriatric memory dysfunction result from neuronal degeneration and reduced cholinergic (acetylcholine-based) transmission (Small & Fodero, 2002). The primary therapeutic approach to date to address the cognitive loss associated with AD has been that of a cholinergic replacement strategy.

The acetylcholine system consists of choline acetyl-transferase, acetylcholinesterase, and muscarinic and nicotinic acetyl-choline receptors. It has since been found that patients with Alzheimer's disease had up to a 90% decrease in acetylcholinesterase and choline acetyltransferase activity (Small & Fodero, 2002). These two enzymes are respectively involved in the degradation and synthesis of acetylcholine.

Since both memory function and attention are improved by increasing both the level and duration of action of the neurotransmitter acetylcholine pharmaceutical management of dementia typically involves the administration of different classes of cholinomimetics (i.e. acetylcholine precursors, cholinergic agonists and acetylcholinesterase inhibitors). Cholinomimetics have been used to enhance attention and memory in experiment animals,

healthy human subjects and Alzheimer disease patients (Freo, Pizzolato, Dam, Ori, & Battistin, 2002). Cholinesterase inhibitors are a class of drugs that improve the effectiveness of acetylcholine either by increasing the amount of it in the hippocampus and the cortex by strengthening the way nerve cells respond to it. The top three cholinesterase inhibitors, Donepezil (Aricept), Galantamine (Razadyne), and Rivastigmine (Exelon) are often prescribed to patients with Alzheimer's disease who are in the moderate stages cognitive decline. The most commonly prescribed treatment is for Alzheimer's disease is Donepezil. Donepezil has been shown to inhibit acetylcholinesterase (AChE) activity in human erythrocytes and increases extracellular acetylcholine levels in the cerebral cortex and the hippocampus of the human and the rat (Kasa, Papp, Kasa & Torok., 2000).

Acetylcholinesterase inhibitors inhibit AChE in hippocampus, thalamus and cortex and prevent the cholinesterase enzyme from breaking down acetylcholine, so increasing both the level and duration of action of the neurotransmitter acetylcholine. In addition, AChE inhibitors improve different cognitive (i.e. visuospatial and verbal) functions in a variety of unrelated disorders such as dementia with Lewy bodies, Parkinson disease, multiple sclerosis, schizoaffective disorders, iatrogenic memory loss, traumatic brain injury, hyperactivity attention disorder and, as we recently reported, vascular dementia and mild cognitive impairment (Freo et al., 2002).

Recent memory studies have shown a relationship between the hippocampus, improved memory function and the use of histone deacetylase (HDAC) inhibitors (Science Daily, 2007). These inhibitors when placed directly to the hippocampus have been shown to enhance memory and synaptic plasticity in the brain. HDAC inhibitors relax the protein structure that organizes and compacts genomic DNA, allowing for easier activation of genes

involved in memory storage. Studies suggest that HDAC inhibitors could boost memory in humans and because of the way they work may be therapeutic for people with both Alzheimer's and Huntington's diseases.

While, it is known that the loss of cholinergic transmission in the brain plays an important part in Alzheimer's disease, it is not the only factor involved. There are also abnormalities in glutamatergic, noradrenergic, serotonergic, and dopaminergic transmission which (Doggrell & Evans, 2003).

Dementia and Neuropsychological Functioning

One of the most difficult problems in the study and identification of dementia is separating the normal effects of aging from the acquired effects of injury or disease. Neuropsychological measures appear to be the most promising to better understand the mechanisms of cognitive impairment, especially when compared to age-based norms. For example, in 1998 the APA Presidential Task Force on the Assessment of Age-Consistent Memory Decline and Dementia stated that neuropsychological tests are among the best measures of dementia. Several researchers in this field have provided strong evidence that neuropsychological testing offers reliable results.

According to Tuokko & Frerichs (2000), the most common predictors of dementia are age and poor performance on measures of memory, verbal fluency and attention. In terms of memory measures, verbal measures are generally thought to be better predictors of dementia than nonverbal measures. Masur, Fuld, Blau, Crystal & Aronson (1990) and Devanand, Folz, Gorilyn, Moeller & Stern (1997) reported that measures of verbal memory have been shown to predict dementia in the elderly. Devanand et al. also stated the best neuropsychological

predictors of dementia are poor performance in verbal memory and categories rather than the subscores of letter fluency and performance as measured by the Wechsler Adult Intelligence Scale-Revised (WAIS-R). Further, Tuokko, Kristjansson, & Miller (1995) reported the verbal measures that reliably predict who will receive a diagnosis of dementia include: scores on the Wechsler Adult Intelligence Scale-Revised Digit Symbol subtest (WAIS-R, 1981); retention and retrieval scores as measured by a modified version of the Buschke Cued Recall (Buschke, 1984) called the 12-Item Selective Reminding Test (Tuokko & Crockett, 1991); and scores obtained from the Wechsler Memory Scale: Information subtest ([WMS] Wechsler, 1975). However, nonverbal measures may be more appropriate for some persons with English as a second language because the administration of the assessment is less confounded by language difficulties.

Additionally, deficits in episodic memory are a reliable predictor of dementia. Studies have shown that deficits on episodic memory were identified at least 5 years before the clinical onset of dementia (Masur, Sliwinski, Lipton, Blau & Crystal, 1994; Tuokko & Frerichs, 2000). Using population-based data, Amieva et al., (2005) reported that abnormally low performances can be evidenced in several domains of cognition, nine years before a clinical diagnosis of Alzheimer's disease. In an epidemiologic sample of participants without dementia, a measure of short, delayed verbal recall and the Wechsler Memory Scale - Information subtest (WMS, 1975) most accurately predicted conversion to Alzheimer disease in seniors after five years (Tierney, Yao, Kiss & McDowell, 2005). Delayed word recall has also been positively associated with decreased hippocampal volume and neuropathologic lesions (Mortimer et al., 2005). With respect to nonverbal memory, Amieva et al. found that scores from the Benton Visual Retention Test ([BVRT] Benton, 1974) for pre-morbid

dementia participants were already significantly lower by 1.8 points than scores for individuals that did not develop dementia.

Of note, however, is that Hultsch et al. (1990) have questioned the reliance of purely psychometric methods to assess cognitive function. They suggest that psychometric measures may not give us an accurate picture of the everyday performance of individuals. Further, Lezak (1995) has suggested that neuropsychologists should ideally strive to utilise both normative comparison standards and individual comparison standards when conducting a neuropsychological assessment. Consequently, striking a balance among the factors for cognitive decline is likely to provide us with a more thorough picture. This should include looking at cognitive function in terms of how a person's ability relates to those of age-matched persons, looking at cognitive ability as reported by a variety of individuals (including those in close relationship with the participant), and considering the amount of change a person has undergone *over time*.

TBI and Dementia

Case-controlled studies suggest that TBI may increase the risk for all dementias (Salib & Hillier, 1997; Luukinen et al., 2005). Other studies have shown there is increased risk for degenerative dementias such as Alzheimer's disease following TBI (Graves et al., 1990; Rasmusson, Brandt, Martin & Folstein, 1995; Salib, 2000; Mortimer, van Duijn & Chandra, 1991; van Duijn, Tanja, Haaxma, Schulte, Saan, Lameris et al., 1992; Mayeux, Ottman, Tang, Noboa-Bauza & Marder, 1993; Guo et al., 2000). There is also evidence that severe TBI before age 65 increases the incidence of dementia (Plassman, Havlik, Steffens & Helms, 2000) as well as the rate of cognitive decline resulting in a diagnosis of Alzheimer's disease

(Gedye, Beattier, Tuokko, Horton & Korsarek et al., 1989). The 1991 meta-analysis of case-control studies of Alzheimer's disease by Mortimer et al. did show a positive relationship between a history of head trauma and Alzheimer's, particularly amongst males. However, not all case-control studies found this relationship (Lindsay et al., 2002; Chandra, Philipose & Bell, 1987; Chandra, Kokmen, Schoenberg & Beard, 1989; Shalat, Seltzer, Pidcock & Baker, 1987; Rasmusson et al., 1995). In fact, contrary to previous reports about the association, the large EURODEM pooled analysis of four European, population-based prospective studies of individuals 65 years and older found no association between head trauma and risk of Alzheimer's disease (Launer et al., 1999). Subsequently, even if research findings do seem to support an association between TBI and dementia later in life, speculation about the precise nature of this association persists (Guo et al., 2000; Plassman et al., 2000; Lye & Shore, 2000).

Factors Mediating the Effects of Brain Damage

Neuronal Reserve & Cognitive Reserve

The general idea of reserve against brain damage stems from the repeated observation that there does not seem to be a direct relationship between the degree of brain pathology or brain damage and the clinical appearance of that damage. The strongest support for reserve is related to studies wherein people meet the neuropathological criteria for AD at autopsy, but did not become demented before death (Katzman, 1993; Snowdon et al., 1997). This suggests that there are attenuating factors that can modify the clinical expression of AD.

Two mechanisms have been suggested to explain these findings: One is neural or brain reserve, sometimes called a 'cognitive reserve' as in Bowler, Munoz, Merskey & Hachinski

(1998). Bowler et al., put forth the term cognitive reserve to refer to more efficient synapses or more active brain reserve. Active brain reserve refers to additional brain circuits that become active when other parts of the brain become too damaged by the plaques and tangles of the disease to function. An area of reserve closely related to that of Bowler et al, was identified by Stern (2002), who reported neuronal or brain reserve, in reference to the amount of damage that can be sustained in a passive manner by the brain (through acquired injury) before reaching a threshold for clinical expression. This type of brain reserve is calculated using measures such as brain size or synapse count. Implicit in the belief of this mechanism is that there is a direct relationship between the quantity of available neural substrate and expressed cognitive ability, and that the total brain reserve capacity remains fairly constant across individuals. This type of brain reserve refers to the synaptic wetware or neural hardware of the brain, and is a concept that is most closely linked to the idea of neural plasticity. Plasticity is a term that is often used to refer to both neural compensation and the ability of the brain to generate new physical and/or functional connections.

Some major animal researchers maintain that the brain has a limited capacity for plasticity (Kolb, 1995; Whishaw, Kolb & Sutherland, 1991; Schallert, 1983). Implicit in this view is that repeated instances of brain damage will sum together and that the ultimate damage has a similar effect on each animal or person. Individual differences shown after acquired brain injury would only be seen when a person has, for example, a larger or smaller brain, a brain anomaly or a previous injury and therefore less or more brain reserve. Further, more damage eventually results in deficit and clinical detection as reflected in Patient #2 below in Figure 2.

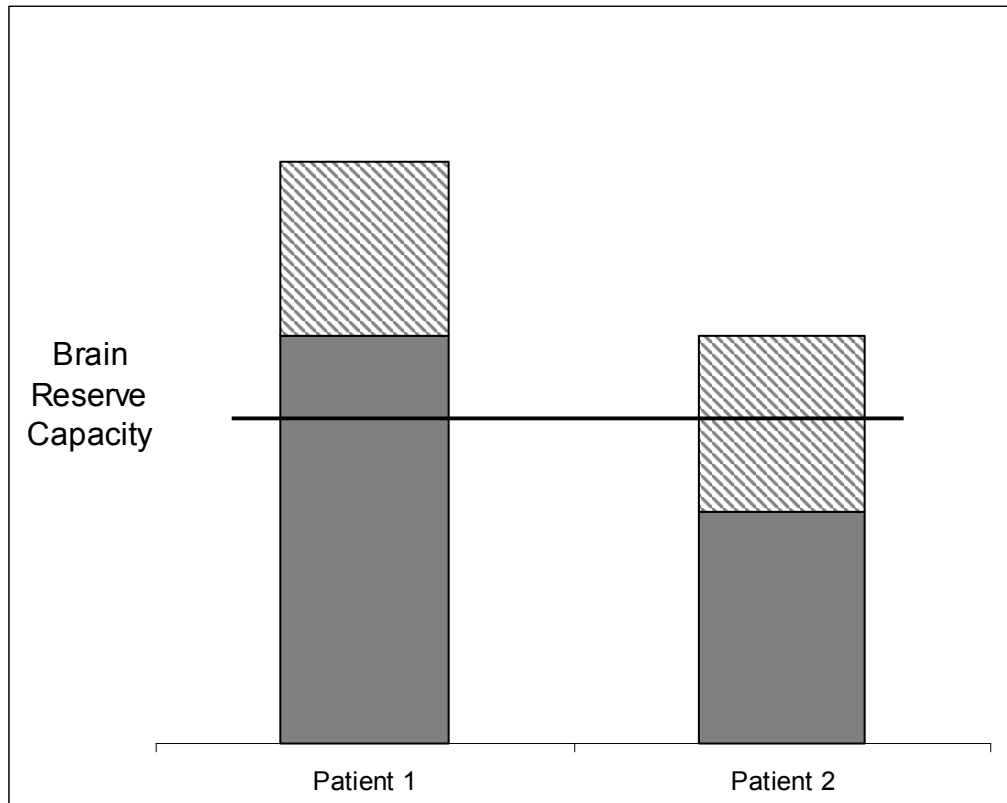


Figure 2. The threshold or neuron/brain reserve capacity model, loosely based on that of Stern (2002).

Figure 2 displays the relation of cognitive functional impairment to neuronal or brain reserve. This could be described as the neural hardware or ‘wetware’ of the brain. The parallel line represents the clinical threshold for cognitive functional deficit. Therefore, two patients with different amounts of brain reserve who have a lesion of the same size (as shown by the striped section) will have different results. Patient #1, an individual with greater neural brain capacity (as shown by the taller bar), could remain unaffected. However, Patient #2, who has less neuronal brain reserve (as shown by a shorter bar), will have a clinical deficit because the damage exceeds the threshold sufficient to compensate for that deficit. Studies of brain volume have supported this model. For example, Mori, Hirono et al. (1997) reported intelligence was correlated both positively with premorbid brain volume and negatively with

magnitude of brain atrophy in patients with AD. They also reported that impairments in language and memory were correlated with magnitude of brain atrophy but not with premorbid brain volume.

The second mechanism of reserve as suggested by Bowler et al. (1998) is increased intellectual activity. The belief is that this activity may enhance brain repair and recovery mechanisms and therefore result in a slower rate of progression of AD. In addition, they propose that other brain regions may ‘take over’ the functions of those affected by the disease. This second type of brain reserve is described by Stern (2002) as a more active process and is *also* called cognitive reserve but in this instance Stern is referring more to the ‘software’ of the brain. He is making reference to an intelligence, a term used here to indicate the capacity for adaptive, efficient, and flexible problem solving as a result of genetic endowment, education and/or experience (2002). Thus, cognitive reserve involves the ability of well-established brain networks to adjust to increased task demands or to compensate for changes resulting from neural disconnection after damage or atrophy. This process is reflected in Figure 3 below.

This second type of reserve is related to compensation, a term typically reserved for a specific response to brain damage, wherein brain structures that are not normally used by an individual prior to brain injury are utilised. In such instances, compensation occurs in order to make up for the damage.

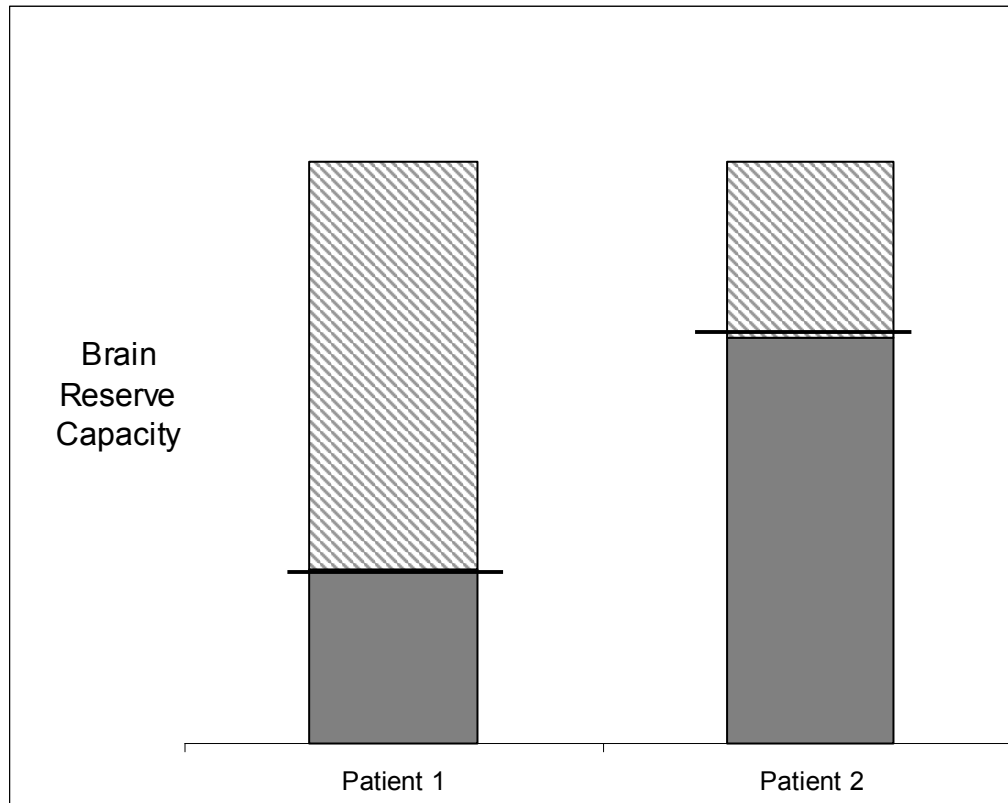


Figure 3. The cognitive reserve model, loosely based on that of Stern (2002).

In Figure 3, two patients have the same amount of brain reserve. However, Patient 1 has less cognitive reserve than Patient 2 (as reflected by the solid area), as such, Patient 2 can tolerate a larger lesion than Patient 1 before functional impairment can be identified clinically. The dotted/lower areas represent the size of a potential lesion that can be sustained prior to the patient reaching the clinical threshold for identification of functional deficit, as shown by the parallel lines. An example of a factor that could contribute to increased cognitive reserve would be years of education.

The model of cognitive reserve presented in Figure 3 is consistent with previous research. For example, Hill et al. (1993), Fratiglioni, et al. (1991), Katzman, 1993 report that there is a higher prevalence of dementia in elders who are poorly educated. Also, greater

general cognitive impairment was found among seniors with less education (Farmer, Kittner, Rae, Bartko & Regier, 1995). These studies support the idea that a neural protective effect exists as a result of increased cognitive reserve related to education. However, active brain reserve as described by Stern is not limited to compensatory functions that are operating during age-related cognitive decline but also in younger individuals with no acquired neural injury (2002).

Additional recent findings from the Nun Study by Mortimer et al. (2005) add support to both models of reserve because they suggested the importance of higher education and larger brain size in masking the underlying disease pathology of AD. The concept of reserve thus assumes two things. First, it assumes that there are individual differences in the capacity for reserve. As such, a higher capacity for reserve through neural or cognitive reserve could be considered a protective factor. By the same reasoning, an apparently intact individual with pre-existing brain damage could tolerate less new brain damage than that tolerated by another individual without pre-existing injury, particularly if the person had a lower level of cognitive reserve. Second, the model assumes that there is a critical threshold, and that once the brain reserve has been depleted and cognitive reserve has been exceeded beyond this threshold (similar to a fixed cut-off point), specific clinical or functional deficits emerge. These models can be used to account for differences in the onset of clinical symptoms. Therefore active cognitive reserve can mediate between the pathology and the expression of clinical outcome, including the severity of clinical symptoms. Further, this can occur after the passive brain reserve threshold has been reached as shown in Patient #2 in Figure 3.

The concept of brain reserve as it relates to memory loss and cognitive impairment has been introduced in this paper to suggest the attenuating function of cognitive reserve (e.g.

years of education) in persons with and without TBI as they age. Also, a distinction has been suggested between brain reserve and the ability to optimise or maximise normal performance, as well as the ability to compensate or attempt to maximise cognitive performance in the face of brain damage using brain structures or networks not engaged when the brain is not damaged.

Summary of the Study

The present study investigates the relationships among TBI, dementia, and cognitive and psychosocial functioning in the elderly. This study uses data drawn from a large Canadian study of changes that take place as people age, including the changes that take place within a sample of individuals with self-reported head injury with loss of consciousness compared to those individuals with no previous TBI injury. A number of specific hypotheses have been derived from the general hypothesis that TBI increases mortality and morbidity, including dementia, and accelerates cognitive impairment in the elderly. In turn, this impairment is associated with psychosocial issues.

Dependent variables include: memory measure scores, collateral reports of general decline, diagnosis of dementia, as well as mortality. Measures were chosen to examine whether seniors with previous TBI have an increased likelihood of decline and/or deficits in cognitive function, and if so, to examine the range from impairment without dementia, to memory problems, to faster decline and dementia, and death. This study also examines whether TBI predicts changes in personality and impaired psychosocial function. These changes are presumed to lead to decreased ability to maintain familial relationships, which in turn lead to an increased likelihood of divorce. Therefore, marital status information of

participants was examined to determine whether the possible psychosocial effects of previous TBI persist with age. Additionally, cognitive reserve in the form of education is explored as a possible mitigating factor for traumatic brain injury.

Method

Sampling Technique

CSHA data source

The data for this project were obtained from the Canadian Study of Health and Aging (CSHA). CSHA is a nation-wide prevalence study of dementia among elderly Canadians (Canadian Study of Health and Aging, 2007). Data were collected at three points in time, approximately five years apart, and thus are known as CSHA-1, CSHA-2, and CSHA-3.

The core objectives of CSHA-1 addressed the prevalence, incidence and risk factors for dementia, as well as the impact of dementia on family caregivers (CSHA Working Group, 1994). The CSHA-2 study explored the clinical course of dementia and the early stages of cognitive loss (CSHA, 2000). CSHA-3 continued to follow patterns of cognitive decline in the participants; however, that data was not available to this researcher. The present study only examines information from the first two data collection points, CSHA-1 and CSHA-2.

During CSHA, participants were living in five geographically defined regions (i.e., Maritimes, Quebec, Ontario, Prairies and B.C.). Sampling included 36 cities and surrounding rural areas across Canada. Trials excluded participants who were living in the Yukon, the Northwest Territories, on Native reserves and in military units.

The CSHA involved two distinct populations of persons: (1) community-dwelling individuals; and (2) residents of institutions. Participants were assessed in 1991-2 (CSHA-1)

and in 1996-7 (CSHA-2), and were 65 or older as of October 1, 1990. They were randomly selected from the Canadian population of those in institutions and those in the community with stratification by age group (65-74, 75-84, 85+) (CSHA Working Group, 1994). Of those who participated in CSHA-1, 87.5% also participated in CSHA-2 (CSHA Working Group, 1998). In all, 9008 community residents and 1,255 residents of institutions were surveyed. All were fluent in English or French.

CSHA community source. The community samples were derived from health insurance databases in four of the regions (CSHA Working Group, 1998). In the fifth region, election and municipal records from the Enumeration Composite Record were used. Individuals were then randomly selected by age group using an optimum allocation procedure to reduce age-related variance in sample groups. The sample included both men and women, regardless of ethnic origin or education. Consenting participants then participated in a screening interview conducted by a nurse.

Following the screening interview, all of the individuals in the community sample who were found to be positive for cognitive impairment on the Modified Mini Mental State examination ([3MS]; Teng & Chui, 1987) (i.e. scored < 78 out of 100 on the 3MS) received a clinical assessment as described below. Additionally, a number of community-living participants who screened cognitively normal and were equal in number to those expected to receive a diagnosis of dementia were also examined clinically (CSHA Working Group, 1998). The total clinical subsample within the overall community sample was 1,659 participants.

CSHA institutional source. Seniors were selected from this group by way of a sample drawn from institutions in each region (N=1,255). The institutional sample in 15 of the 18 CSHA centers was derived from sampling frames that merged nursing homes, chronic-care

facilities, and collective dwellings such as convents (CSHA Working Group, 2000). The institutions were first stratified by size (<25 beds, 26-100 beds, and > 100 beds). Then seventeen institutions were randomly selected in each of the five study regions, and participants were then randomly selected from the institutions. The availability of provincial insurance databases allowed three of the eighteen study centers to randomly select their institutional patients directly. The high prevalence of dementia in the institutions made screening redundant. Therefore all institutional participants underwent the clinical component. Since this clinical assessment was administered to all selected capable participants living in institutions and since, for those who were not deemed testable (3MS score < 50), information was provided by collatorals and clinicians (3MS score < 50), it is believed that the sample population from the institutions was fairly represented.

The Clinical Component for CSHA

The clinical component of the CSHA was designed to explore further the presence of cognitive impairment and dementia in those who had tested positive for clinical impairment (< 78) using the 3MS during the screening process. Part of the clinical assessment included the completion of risk factor questionnaires that collected information on personal history, health and family history, including whether the person had previously sustained a head injury with loss of consciousness. Information on risk factors at CSHA-1 was collected in two ways. A random sample of 1,628 participants who were screened and found to be cognitively normal at CSHA-1 completed a risk factor questionnaire themselves. For participants whose cognitive problems prevented them from providing accurate information, a person who knew the individual well (typically, the spouse or other family member) completed the

questionnaire. These collateral informants also provided input about the cognitive and functional status of each participant.

The clinical examination for both CSHA-1 and CSHA-2 included extensive medical and neuropsychological assessment. Each individual's cognitive status was then determined by a multidisciplinary consensus process (CSHA Working Group, 1994).

The clinical examination in CSHA-1 and 2 included the following steps:

1. A nurse re-administered the 3MS, tested hearing and vision, recorded vital signs, recorded height and weight, and collected information on medications as well as information from self-assessed and proxy risk factor questionnaires (e.g. having sustained a previous head injury with loss of consciousness). Additionally, based on information obtained from the collateral informant, cognitive and functional status was assessed further using the Cambridge Examination for Mental Disorders ([CAMDEX]: Roth, Huppert, Tym & Mountjoy, 1988);
2. A physician took a medical history and performed a neurological examination;
3. A psychometrist administered neuropsychological tests to all subjects deemed testable (3MS score > 50). The results were later interpreted by a neuropsychologist;
4. The physician and neuropsychologist independently made preliminary diagnoses and then met with the nurse to reach a 'consensus diagnosis'. The criteria used to determine this diagnosis are provided below.

Diagnostic classification for CSHA

Diagnoses included no cognitive impairment (NCI), cognitive impairment but not demented (CIND), and dementia. Diagnoses of dementia included possible or probable

Alzheimer's disease, multi-infarct dementia, other dementia (e.g. Parkinson's dementia, and Pick's disease), and unclassified dementia. A diagnosis of CIND and NCI were made via clinical judgment, and a diagnosis of dementia at CSHA-1 was made according to the criteria in the Diagnostic and Statistical Manual of Mental Disorders, third edition, revised. [DSM-III-R] American Psychiatric Association, 1987) (CSHA Working Group, 1994). During CSHA-2, differential diagnoses used criteria given for Alzheimer's disease and DSM-IV criteria given for Alzheimer's disease according to the NINCDS-ADRDA (National Institute of Neurological and Communicative Diseases and Stroke/Alzheimer's Disease and Related Disorders Association). Finally, criteria from the ICD-10 (International Classification of Diseases) and the NINDS-AIREN (National Institute of Neurological Disorders and Stroke and Association Internationale pour la Recherche et l'Enseignement en Neurosciences) were used to define vascular dementia (CSHA Working Group, 2000). As part of the reporting of the prevalence of dementia in the CSHA participants, data pertaining to whether particular participants had dementia while living either in the community or within institutions was selected in a case-control manner from the summary data produced by the CSHA Working Group (1991).

Neuropsychological Tests Used During CSHA

The CSHA study was essentially diagnostic in nature and focused on assessing the incidence and specific risk factors for dementia in seniors. Therefore, neuropsychological measures were selected for the original CSHA study that: 1) reflected the neuropsychological constructs described in the Diagnostic and Statistical Manual for Mental Disorders, third edition, revised (DSM-III-R); 2) had normative data available for the elderly; and/or 3) were

familiar to psychologists. The tests administered in CSHA were designed to tap areas of memory as well as abstract thinking, judgment, aphasia, apraxia, agnosia and construction (CSHA-2 Working Group, 1998).

The current study utilised a sample of the memory tests available within the CSHA battery since such neuropsychological test scores have been suggested to be of value for predicting and measuring cognitive deterioration. Further, cognitive measures were selected if they had previously established psychometric validity and were believed to measure aspects of interest within the realm of long-term memory systems. Specifically, episodic verbal memory, as well as, episodic nonverbal memory were explored. Many of the tests selected from those used in the CSHA study yielded multiple measures of memory functioning; therefore, selected memory scores were used during the current study. A rationale for the selection of measures and a description of each memory measure is provided below.

Current Study - Participants

For the current study, participants were retrospectively selected from those who had taken part in CSHA-1 and CSHA-2. They included both community-living seniors who screened positive and negative for cognitive impairment as well as institutional residents who underwent clinical assessment (N=2914). Head trauma was the case-based selection variable and is defined as those individuals who underwent clinical assessment in CSHA and who self reported or were reported by clinicians to having sustained a traumatic injury to the head from an accident, fall or otherwise and resulting in a loss of consciousness (LOC). This information was collected from a risk factor questionnaire on medical and family history that

participants completed in the presence of a nurse during the clinical history component of the CSHA study.

The sample for this study consisted of 269 elders with a self-reported history of head injury. However, because information regarding level of education was missing for nine of the participants, they were removed from the study, resulting in a total sample of 260 participants (males =139, females = 121). Of those who were identified as having sustained a previous head injury, 106 were living in institutions at CSHA-1 and 154 were living in the community. These seniors (referred to in the current study as TBI) were then matched to 520 persons selected from the CSHA study who were of the same gender, age and years of education as the TBI participants, but who did not report a history of head injury resulting in a loss of consciousness. Of those who were identified as not having sustained a previous head injury, 167 were living in institutions at CSHA-1 and 353 were living in the community.

Matching procedure

The matching procedure began by retrospectively removing those persons with a self-reported history of head injury with loss of consciousness (N=260) from the larger clinical data set of CSHA. The rest of the clinical (nonTBI) data set was then separated into two further data sets based on gender, consisting of 828 males and 1574 females that were used for potential matching to the 139 males and 121 females in the TBI data set. A listing was then created for each gender-based data set by age and education in years. Following this, each TBI participant was hand-matched to two persons of the same gender from the nonTBI groups by using age and then education to match the two groups. Finally, all case and contrast participants selected were gathered back into a single data set.

Two nonTBI participants were matched to each TBI survivor because it was anticipated that there would be much greater variability amongst those in the comparison group. Further, it was anticipated that this within group variability would be reduced by averaging the relative variance contribution from each control participant through the process of matching 2:1. In cases where there was no exact match by age or education, a person with the next closest age or education was chosen as a match. This process was alternated so that if a slightly older person was matched in one case, then the next time a next closest match was made, a slightly younger person was matched, thus any differences created by imperfect matches would be evened out. No distinction was made during the random selection of nonTBI matches between those who were community living versus those who were institutionalised in that control participants were not matched to TBI cases based on living situation.

The matching procedure was undertaken so that control participants and cases are similar in characteristics which may be related to the variables examined but these characteristics were not of interest in themselves. As such, the matching variables were chosen because they were believed to have the greatest likelihood of influencing the results. For example, research cited earlier in this paper supported the notion of education having an influence on one's cognitive reserves and ability to compensate for deficits. Additionally, some gender-based differences have been displayed in studies where researchers examined cognitive abilities in the elderly. Finally, research has shown that age is strongly associated with a diagnosis of dementia. As such, this writer chose to hold these variables constant during the comparisons in an attempt to isolate a "traumatic brain injury effect". Otherwise, this effect might be masked by the influence of education, gender, and/or age. However, this

method did not give consideration to other possible covariates during the matching process such as substance abuse, chronic physical conditions or mental illness.

Measures

Memory measures of the current study

Measures of memory were selected from the original CSHA neuropsychological test battery in order to capture a variety of aspects of explicit long-term memory (LTM) in the current study. Measures included long-term memory as captured by the Wechsler Memory Scale Information Subtest, ([WMS]; Wechsler, 1975); episodic memory as measured by a modified version of the Buschke Cued Recall Test ([Buschke]; Buschke, 1984); and, Rey Auditory Recognition Scores ([RVLT]; Rey, 1964). Additionally, episodic nonverbal memory scores as measured by the Benton Visual Retention Test ([BVRT]; Benton, 1974) were utilised. Participants' explicit long-term memory measures were chosen because they were believed to be the most sensitive to the cognitive effects of acquired brain injury, as opposed to implicit memory functions which were shown to be more resilient (Craik & Jennings, 1992). In each instance, data from both points in the CSHA data collection process were utilised.

Semantic memory (LTM). The Wechsler Memory Scale: Information Subtest ([WMS]; Wechsler, 1975) has been identified as an acceptable measure of explicit long-term verbal memory function (CSHA Working Group, 1994; Spreen & Strauss, 1998). This subtest is comprised of simple questions that assess whether the participant is oriented to age, date of birth, government officials, time and place. The six-item subtest has been declared a reliable general predictor of cognitive decline in an elderly population (Tierney, 1996). This test was

selected for the current study because it assesses long-term recall of participants (CSHA Working Group, 1998). However, it could be argued that the WMS is more accurately a measure of semantic memory because while the questions include conceptual and factual knowledge, the information is so over learned (i.e., what is your birthdate? Who is the Prime Minister of Canada?) that the individual may have forgotten where they learned the information originally, thus making it more accurately a measure of semantic memory than episodic. The participants' total raw scores from the WMS: Information subtests were used in this analysis.

Episodic memory – verbal. Explicit, verbal tests of episodic memory include a modified version of the Buschke Memory Test (Buschke, 1984) called the Buschke Cued Recall or the Buschke Selective Reminding Procedure, as modified by Tuokko & Crockett (1991). The Rey Auditory-Verbal Learning Test ([RAVLT]; Rey, 1964) was also selected as a measure of episodic verbal memory.

The Buschke is based on a selective reminding procedure of a list-learning task. The Buschke was chosen because it is a measure of verbal episodic memory that offers both cued and free recall. Buschke originally developed this measure so that three different channels were employed to assist in encoding (i.e., visual pictures, category cues and naming). In so doing, he hoped to minimize apparent memory deficits that are due to cognitive processes other than memory and that decline with normal aging (Grober & Buschke, 1987). Specifically, free recall is more effortful for older persons (Macht & Buschke, 1983). Cued encoding and recall help to minimize apparent memory deficits because providing cues during learning and retrieval lessens the cognitive effort required by older adults (Grober & Buschke). Since the 1994 paper by Tulving et al. demonstrated the importance of the level of

processing information in long-term memory, other researchers have shown that the deeper the level with which information is processed when encoded, the greater the possibility of retrieving it from long-term memory (e.g. Tuokko & Crockett, 1991; Tuokko, Vernon-Wilkinson, Weir & Beattie, 1991). Further, utilising semantic cues during encoding and the same cues at retrieval increase the performance at delayed recall.

Briefly, the Buschke selective reminding procedure involved asking the participants to look at a page (8.5" x 14") of line drawings of 12 common objects. Participants were then asked to point to and name each of the 12 drawings that correspond to the semantic category given (e.g., one of these is a piece of fruit). After the initial searching and naming procedure was completed, the participant was asked to count backward from 100 by 1s for 60 seconds. Next, they were asked to recall all of the objects that were previously presented. The category clue was given for any objects not recalled freely. After an incorrect response or no response to the category cue, the picture array was presented again, and the search procedure was completed only for those objects not correctly identified by cued recall. The procedure was completed without distracters or delays among subsequent trials. In total, participants were asked to recall the information in three learning trials, with the second and third completed after a delay of approximately 15 minutes, during which time nonverbal tasks were performed. During the delayed recall trial, participants were given an opportunity to freely recall as many of the objects as possible and, as in the first trial, they were given category cues for objects not freely recalled. Participants were not informed that they would be required to remember the information presented and they were not informed of the delayed recall trial. The total number of words identified after a delayed free recall and cued recall (i.e., delayed total recall) was used in the current study. Tuokko et al. (1991) explored the early identification of

dementia using scores derived from the Buschke and reported that retrieval or the sum of words identified by way of free recall over three trials is the best a priori predictor of dementia in that accurate prediction for the development of dementia would be achieved 62% of the time. Following a later study by Tuokko et al. (1995) the researchers reported that both the retrieval and retention (defined as total words identified by way of free and cued recall after a delay) were among the measures most significantly related to a diagnosis of dementia or no dementia. In the current study, the total delayed free and cued recall was chosen mainly because these results have been described by (Hänninen, 1996) as being the least variable and most stable scores of the test. Further, disturbances of mood, depression in particular, is a common outcome after mild to moderate TBI (Alexander, 1995). A study by Brown, Scott, Bench & Dolan (1994) suggested that the free recall of word lists, particularly after a delay, are more sensitive to the cognitive decline associated with depression in seniors than are tests of cued recall after a delay. Another study by Hill, Stoudemire, Morris, Martino-Saltzman & Markwalter (1993) also suggested that using memory tasks that enhance semantic associations through cueing are better able to reveal real memory impairment associated with dementia as opposed to depression-related cognitive dysfunction in that participants with actual dementia are unable to use the cues to enhance their recall of words.

The Rey Auditory Recognition Test (RAVLT) is also a test of episodic verbal learning and memory. It consists of 15 nouns read aloud over five trials with each trial being followed by a free-recall test. After the fifth trial there is an interference list of 15 words followed by a free-recall test of that list. Then there is another trial of the original list of words without their having been read again. After a delay, there is a recognition task wherein 30 words are read out loud and the participant is then asked to identify those words from the original list. Two

scores are then calculated, one called true positive recognition, or the number of words correctly recognised, and the other called true negative recognition, or the number of words incorrectly recognised. The true positive recognition and true negative recognition total raw scores of this measure were chosen from the total five-trial scores for analysis because they reflect verbal learning.

Episodic memory – non verbal. Additionally, the Benton Visual Retention Test (BVRT) Benton, 1974), a nonverbal test of episodic memory, was selected for use in the current study. The BVRT is used primarily to assess visual memory and visual perception abilities (Spreeen & Strauss, 1998). This measure has been shown to differentiate between normal elderly and elderly with dementia. A participant is instructed to study a card with a design on it for ten seconds. When the card is removed the person is shown another card with four different designs on it, one of which was the original design. The participant then indicates which of the four designs was shown previously. Total correct raw scores of this measure were included in the current study. This variable was chosen because it is a nonverbal test of recognition and is important because it provides an additional measure of memory that is less sensitive to participants for whom English or French is not their first language.

The scores obtained by TBI participants on the measures listed above were compared to those without previous TBI to determine if there was an overall effect of TBI on the memory test scores. If an overall memory effect was identified statistically, additional comparisons were made for the two groups (those with and without TBI) on each memory test score.

Psychosocial measures

For the current study, the use of psychosocial measures was limited to the consideration of the marital status of the participants only. This information was collected during the personal and medical history section of the Risk Factor Questionnaire completed at CSHA-1 (CSHA, 1994). The information was completed by the participant, or if the participant was not capable of completing it, by a person who knew the participant well. An additional post hoc measure of living situation (e.g. lives alone) was captured from the Community Living Questionnaire, the Institutionalisation Questionnaire and the Decedent Questionnaire residential history questions conducted at CSHA-2 (CSHA, 2007). These questionnaires were completed by the participants, or if they were not capable, the information was collected during an interview or over the phone.

Collateral Reporting of Cognitive Decline

The cognitive status of participants in terms of assessed ‘intellectual functional loss’ was selected from a standardised clinical schedule within the interviewer summary section of the Cambridge Mental Disorders of the Elderly Examination ([CAMDEX] Roth, Huppert, Tym & Mountjoy, 1988) at CSHA-2. The CAMDEX consisted of three main sections: A structured clinical interview of the participant, conducted by a nurse to obtain systematic information about the present state, past history and family history; a range of objective cognitive tests which constitute a mini-neuropsychological battery; and a structured interview with the participant’s relative or other informant to obtain independent information about the participant’s present state, his or her functioning during the past five years and family history.

Following this, a clinical summary for different categories of functioning was completed by the interviewer. This measure was selected for the current study because it provides an additional summary rating of the cognitive and functional status of the participant and because it was completed with information from the participant, objective testing and information from someone who knew the participant well.

Years of Education

For the purpose of this study, participants were divided into 3 groups: those with up to grade 7 education, those with some high school education and those with some college/university. Educational cut off points were intuitively selected based upon naturally occurring transition points (i.e., primary/elementary school, secondary/high school, post secondary school/college/university).

Mortality

Information regarding the date of death for participants that died during the CSHA studies, previously obtained from the Registrar of Vital Statistics in each province at CSHA-2, was utilised in the current study.

Data Analysis

The data were analysed using SPSS version 10 and SPSS version 14 for Windows (SPSS, Inc, Chicago, IL, USA.). Univariate analyses conducted using Pearson's Chi-square analyses were performed using the SPSS cross-tabulation function. Relationships between categorical variables were analysed using the Pearson's Chi-square and the Fisher's Exact

test. Other analyses utilised the independent samples t tests. A repeated-measures multivariate analysis of variance (MANOVA) was completed for the memory measures. This was followed by univariate tests if statistically warranted. A repeated measures design was used for the memory measures to reduce the variability among the participants due to individual differences in the error term. This made the design more powerful and, for this reason, Stevens (2002) recommends that researchers seriously consider the use of repeated measures designs where appropriate. The association between education, TBI and diagnosis of dementia was completed using general loglinear analysis by way of the Newton-Raphson method and a Poisson distribution.

For some hypotheses listed below, the level of significance was set at $p < .1$ for one-tailed/directional tests. The probabilities were only located in one tail of the distribution if there was a firm and logical prediction about the direction of deviation from the null hypothesis. For example, it was not anticipated that a previously sustained head injury with loss of consciousness would have a positive effect on a participant's cognitive function or memory. For the remaining hypotheses, that is, those that predicted a difference between the TBI and nonTBI groups, two-tailed tests with a standard level of significance set at $p < .05$ were utilised.

The participants of the current study were not diagnosed or treated as a result of the findings of this study. However, in consideration of the clinical implications of the study, there was an effort to minimize excessive Type I error rates to avoid the possibility of being too liberal and rejecting the null hypotheses and for example claiming that there is a difference in the cognitive functioning of survivors of TBI from the that of persons who have not sustained a TBI, when in reality there is no difference. Clark (1976) believes that because

there is a prejudice on the part of researchers to only report significant results, Type I errors, once made, “are very difficult to correct”. According to Clark’s perspective, the danger to science from a Type I error is much more serious than that of a Type II error because in Type I errors, highly significant results appear definitive and tend to discourage further investigation. Clark also stated that because of this, a stray Type I error can indeed be catastrophic (1976). It is common for most research to accept a Type I error rate of one in twenty, or 0.05, as was used in this study. Therefore, a relatively conservative approach was taken in the data analysis. This was reflected in the requirement of a significant result on omnibus tests of memory prior to conducting univariate analysis of individual memory measures. This was done to address concerns regarding the use of fragmented univariate tests which are also believed to lead to a greatly inflated overall Type I error rate, that is, the probability of at least one false rejection of the null (Stevens, 2002).

To balance the risk of a Type II error and avoid being too conservative, no transformation of data was utilised (e.g. bonferonii correction). A Type II error is only an error in the sense that an opportunity to reject the null hypothesis correctly has been lost. In the case of this study, a Type II error would mean incorrectly dismissing any difference between those with TBI from those without TBI on measures of cognitive functioning (as reflected in the hypotheses below), when in fact there is a difference.

Hypotheses

Morbidity

1. *Diagnosis of dementia.* TBI predicts increased likelihood of dementia. Therefore, more seniors with TBI will receive a diagnosis of dementia at CSHA-1 and CSHA-2 than nonTBI.
2. *Diagnosis of cognitive impairment, not dementia (CIND).* TBI predicts increased likelihood of CIND. Therefore, more seniors with TBI will receive a diagnosis of CIND at CSHA-1 and CSHA-2 than nonTBI.
3. *Neuroprotective effect of education.* Cognitive reserve predicts a decreased likelihood of cognitive decline. Therefore, seniors with TBI and with higher levels of education will have: lower likelihood of diagnosis of dementia, reported cognitive decline, and death at CSHA-2 than TBI with lower education levels.
4. *Earlier diagnosis of dementia.* TBI predicts earlier onset of cognitive decline. Therefore, seniors with TBI who receive a diagnosis of dementia at CSHA-1 or CSHA-2 will be younger than nonTBI.
5. *Earlier diagnosis of CIND.* TBI predicts earlier onset of cognitive decline. Therefore, seniors with TBI who receive a diagnosis of CIND at CSHA-1 or CSHA-2 will be younger than nonTBI.
6. *Lower memory measure scores.* TBI predicts lower memory measure scores. Therefore, more seniors with TBI will have lower memory measure scores from CSHA-1 to CSHA-2 than nonTBI.
7. *General intellectual decline, with input from collateral.* TBI predicts more intellectual decline. Therefore, more seniors with TBI will be rated with general intellectual decline at CSHA-2 than nonTBI.
8. *Increased divorce.* TBI predicts changes in personality and impaired psychosocial function. These changes are presumed to lead to decreased ability to maintain familial relationships, which in turn lead to an increased likelihood of divorce. Therefore, more seniors with TBI will be divorced at CSHA-2 than nonTBI.

Mortality

9. *Increased death.* TBI predicts increased likelihood of death. Therefore, more seniors with TBI will have died at CSHA-2 than nonTBI.

Results

Description of the Study Population

The TBI sample consisted of 260 persons whereas the nonTBI sample had 520 participants. The TBI and nonTBI groups were matched by gender. This resulted in 139 TBI males matched to 278 nonTBI males and 121 TBI females matched to 242 nonTBI females.

The number of TBI males and females compared to those who reported no TBI is shown in Table 1. A Pearson's Chi-square analysis indicated that gender and TBI group are independent of each other because the proportion of males and females remains the same for both groups; thus, the two groups are adequately matched by gender

$\chi^2 (1, N = 780) = 1.00, p = 1.00.$

Table 1

TBI and nonTBI Participant Groups by Gender

Group	Males	Females	Total
TBI	139	121	260
nonTBI	278	242	520
Cumulative Percent	53.5	46.5	100
Total	417	363	780

The TBI and nonTBI groups were also matched by age and years of education at CSHA-1 as shown in Table 2. An independent samples t-test revealed little difference in age between the two groups $t(778) = -.074, p = .941, n.s., 95\% CI = -1.17 - 1.08$. The mean age of participants who reported head trauma with loss of consciousness at CSHA-1 was 78.56 years and the mean age of those who reported never having had TBI was 78.52 years.

At CSHA-2, the mean age of those not deceased who reported previous TBI was 81.59 ($N = 142$), and those not deceased who reported no previous TBI was 81.92 ($N = 286$). An independent samples t-test confirmed no significant difference in mean age between the two groups at CSHA-2 $t(426) = -.466, p = .642, n.s., 95\% CI = -1.69 - 1.04$.

The matching of TBI and nonTBI participants for years of education also appeared successful in that there were only minor differences between groups. The mean education years for the TBI cases was 8.97, whereas the mean education years for nonTBI participants was 8.80 years. This indicates that there was less than two months difference in the mean years of education between the two groups.

The differences in education years between the groups was not significant: $t(778) = -.545, p = .586, n.s. 95\% CI = -.76 - .43$. The years of education ranged from 0 to 22 years for the TBI group, and 0 to 23 years in the nonTBI group. These figures are reflected in Table 2.

Table 2

TBI and nonTBI Participants by Age and Years of Education

Group		Age of Participant at CSHA-1	Age of Participant at CSHA-2	Years of Education
Cases (TBI)	Mean	78.56	81.92	8.97
	SD	7.53	6.76	4.10
	Minimum	65	70	0
	Maximum	102	97	22
Controls (nTBI)	Mean	78.52	81.59	8.80
	N	520	28	520
	SD	7.54	6.81	3.94
	Minimum	65	70	0
	Maximum	101	100	23

The distribution of education by ranges (primary, secondary, college/university) for each group is presented in Table 3. These ranges were created for this study to test hypotheses related to the neuroprotective effect of education.

Table 3

Education Ranges for TBI and nonTBI Participants

	Education Range in Years		
	Primary 0-7	Secondary 8-12	College/University 13+
TBI	91	135	34
% of TBI	35	52	13
nonTBI	178	280	62
% of nonTBI	34	54	12
Total	269	415	96
Cummulative%	34.5	53.2	12.3

Morbidity

Hypotheses 1-2

To explore whether TBI is a risk factor for diagnosis of cognitive impairment and dementia in seniors, a Pearson's Chi-square analysis was performed to see if diagnosis of cognitive impairment is independent of TBI group. The analysis compared 'summary clinical diagnosis', defined as diagnoses related to the presence or absence of cognitive impairment and dementia at CSHA-1 and CSHA-2, with TBI. To explore Hypothesis 1, those participants with a diagnosis of dementia at CSHA-1 were excluded from the analysis at CSHA-2 to eliminate the possible confounding of previous diagnosis of dementia on the totals. This was achieved by only counting new cases of dementia rather than mistakenly counting cases previously identified at CSHA-1, again at CSHA-2. This technique was also used for the analysis of Hypothesis 2, so that those seniors with a diagnosis of CIND at

CSHA-1 were excluded from the analysis at CSHA-2 to eliminate the possible confounding of the effects of previous CIND on the likelihood of their receiving a second diagnosis of CIND at CSHA-2.

When the diagnostic categories were collapsed into those with and without dementia (i.e. no cognitive impairment, cognitive impairment without dementia-CIND were identified as 'not demented' and all dementias were grouped together as 'demented') and a Pearson's Chi-square analysis was undertaken, the one-sided Fisher's Exact Test showed no significant relationship between diagnosis of dementia at CSHA-1 or CSHA-2 and TBI group at the $p < .05$ level $\chi^2 (1, N = 780) = .360$, n.s., $\chi^2 (1, N = 439) = .311$, n.s. respectively.

When the categories were not collapsed (i.e. Probable AD, Possible AD, Vascular Dementia, other dementia, CIND, No Cognitive Impairment) and a Pearson's Chi-squared analysis was undertaken, there was also no relationship between TBI and diagnosis at CSHA-1: $\chi^2 (6, N = 780) = 7.379$, $p = .287$, n.s. Neither was there an association found at CSHA-2: $\chi^2 (6, N = 334) = 10.599$, $p = .102$, n.s. The expected values of the cross-tabulation at CSHA-1 for the categories that were not collapsed showed that there were less TBI with no cognitive impairment than expected and less with probable AD than expected. There were more TBI with CIND and Possible AD and vascular dementia than expected at time one; however, overall, there was no significant differences in the groups. Additionally, at CSHA-2, based on the expected values of the cross-tabulation, there were more TBI diagnosed with CIND than expected and more with vascular dementia than expected but again, the overall differences between the two groups were not significant. The percentages for each subcategory of dementia diagnosis by TBI group are displayed in Table 4, while the percentages of persons diagnosed with dementia and CIND at CSHA-1 are shown in Table 5.

Table 4

Expected and Observed Counts of Diagnosis of Dementia for TBI and nonTBI participants at CSHA-1 and CSHA-2

Diagnosis		Expected and Observed Counts					
		CSHA-1		CSHA-2		Total	
		TBI	nonTBI	TBI	nonTBI	TBI	nonTBI
Normal	Count	90	195	39	77	129	272
	Expected	95	190	38	78		
CIND	Count	84	162	33	61	117	223
	Expected	82	164	31	63		
Probable Alzheimer's	Count	23	60	10	44	33	104
	Expected	28	55	18	36		
Possible Alzheimer's	Count	23	39	10	18	33	57
	Expected	21	41	9	19		
Vascular Dementia	Count	17	37	11	10	28	47
	Expected	18	36	7	14		
Other Dementia	Count	15	13	4	4	19	17
	Expected	9	19	3	5		
Unclassified Dementia	Count	8	14	3	10	11	24
	Expected	7	15	4	9		

Table 5

Prevalence of Dementia and CIND at CSHA-1

Group	Percentage of Participants Diagnosed	
	Dementia	CIND
TBI	33	32
nonTBI	31	31

Post Hoc Analysis

An additional post hoc analysis was conducted to explore the findings above in a more thorough manner. The post hoc calculation was conducted using the Chi-square analysis to explore the status of participants at the point of entry at CSHA-2. This ‘point of entry’ data was taken from information collected by way of the residential history responses to the community interviews, the Institutionalization Questionnaire and the Decedent Questionnaire. This variable identified the participant’s cognitive status (demented or not), and whether the person was still alive, living in the community or in an institution at participant intake CSHA-2. This analysis also utilised the Chi-square analysis and the observed and expected counts feature. However, analysis of these responses indicated no statistically significant association between status at CSHA-2 and group: $\chi^2 = (4,780) = 8.261, p = .082, n.s.$ Observed and expected counts taken from SPSS cross-tabulation are shown in Table 6. The living status for participants at point of entry to CSHA-2 is broken down by percentage for each group in Table 7.

Table 6

TBI and nonTBI Participant Status at Point of Entry to CSHA-2

Status at CSHA-2		Expected and Observed Counts		
		TBI	nonTBI	Total
In Community Not Dead	Count	109	260	369
	Expected	123	246	369
In Institution Without Dementia	Count	41	50	91
	Expected	30	61	91
Dead – No Dementia	Count	24	47	71
	Expected	24	47	71
Demented	Count	61	110	171
	Expected	56	115	171
Dead and Dementia	Count	26	52	78
	Expected	26	52	78
Total Count		260	520	780

Table 7

Percentage Breakdown for Living Status of TBI and nonTBI Participants at Point of Entry to CSHA-2

Living Status at CSHA-2	TBI	nonTBI
In community Not demented	41.9	50.
In institution Without dementia	15.8	9.6
Dead No dementia	9.23	9.03
Demented	23.5	21.2
Dead and Dementia	10.0	10.0

Hypothesis 3

To explore whether education reduces the likelihood of cognitive decline in seniors with previous TBI, the relationship between years of education, diagnosis of dementia, intellectual decline and incidence of death were explored. The analysis utilized a general log-linear model in SPSS and a Poisson distribution to explore the frequency counts of observations falling into each cross-classification category. In this analysis, the participant's education level (primary, secondary, university/college), a diagnosis of dementia, CAMDEX rating of intellectual decline and death were factors in the model. The differential diagnosis categories of dementia were collapsed into one cell in order to maintain a statistically reasonable cell count. This procedure was completed at CSHA-2. However, there were no

significant associations between TBI, education level, diagnosis of dementia, intellectual decline or death: $z(18,780) = -.286, p = .775, n.s. 95\% CI = -1.22 - .913$

Hypotheses 4-5

To explore whether TBI is a risk factor for earlier diagnosis of cognitive decline in seniors, the mean age of only those participants who received any diagnosis of dementia or CIND was compared with the TBI and nonTBI groups using an independent samples t test. The mean age of TBI participants who received a diagnosis indicative of cognitive decline was 80.79, $SD = (8.21)$, while the mean age for nonTBI participants was 80.56, $(SD = 7.30)$. Therefore, the results of this analysis revealed no significant differences in age for those TBI participants diagnosed with dementia or CIND at CSHA-1: $t(247) = -.229, p = .819 95\% CI = -2.23-1.77$.

The mean age of only those participants who received any new diagnosis of dementia or CIND at CSHA-2 was also compared with the TBI and nonTBI groups using an independent samples t test. The mean age for TBI cases who received a new diagnosis indicative of cognitive decline at CSHA-2 was 82.68, $(SD = 6.42)$, while the mean age for nonTBI with a new diagnosis of cognitive impairment or dementia was 83.64, $(SD = 6.83)$. Therefore, the results of this analysis revealed no significant differences in age of those newly diagnosed with dementia or CIND at CSHA-2 either, based on group $t(147) = .823, p = .412 95\% CI = -1.34 - 3.25$. The results of these two analyses are presented in Table 8.

Table 8

TBI and nonTBI Mean Age for New Diagnosis of Dementia or CIND at CSHA-1 and CSHA-2

Group	Mean Age at Diagnosis (Standard Deviation)	
	CSHA-1	CSHA-2
TBI	80.79 (8.21)	82.68 (6.42)
nonTBI	80.56 (7.30)	83.64 (6.83)

Hypothesis 6

The central feature of dementia is impaired memory. To explore the effects of TBI on memory over time, a repeated measures multivariate analysis of variance (MANOVA) was performed using total scores obtained on each of the memory indices (Wechsler Memory Scale Information Subtest, Buschke's Total Recall Scores, Benton Visual Retention Scores, Rey Auditory Recognition Scores). This analysis was completed for both CSHA-1 and CSHA-2 for both the TBI and nonTBI groups. The results suggest that memory scores declined reliably in both groups over the 5-year period (Wilks = .637, $F(5, 128) = 14.559$, $p = .000$). However, an omnibus analysis indicated that there were no group differences on the memory measures at CSHA-1 or over time: Wilks = .974, $F(5, 128) = .681$, $p = .638$, Wilks = .933, $F(5, 128) = 1.84$, $p = .110$, respectively. On the other hand, univariate tests of individual memory measures did indicate significant differences between groups for the Wechsler Memory Scale Information Subtest Score: $F(1, 128) = 6.88$, $p = .010$, and the

Buschke Cued Recall Total Scores (Free and Cued): $F(1,128) = 4.70, p = .032$) at CSHA-2 only. The memory mean scores by group at CSHA-1 and CSHA-2 are shown in Table 9.

Table 9

TBI and nonTBI Mean Scores of Memory Measures at CSHA-1 and CSHA-2

Group	Measure	N	CSHA-1	N	CSHA-2
TBI	Wechsler Info Subtest ^a	189	4.40	66	3.83
	Buschke total delayed ^b	190	13.90	63	11.17
	Rey true positives	178	15.93	61	12.61
	Rey true negatives	178	16.26	61	12.93
	Benton Visual Retention	184	13.77	62	10.11
nonTBI	Wechsler Info Subtest ^a	378	4.35	125	4.18
	Buschke total delayed ^b	376	13.38	122	11.39
	Rey true positives	345	17.22	111	12.91
	Rey true negatives	345	17.02	111	12.91
	Benton Visual Retention	368	13.35	116	10.24

^a = significant differences between TBI and nonTBI at CSHA-2 $p = .01$

^b = significant differences between TBI and nonTBI at CSHA-2 $p = .032$

Hypothesis 7

TBI may be a risk factor for general intellectual decline beyond that associated with normal aging. However, the Chi-square analysis and Fisher's Exact Test:

$\chi^2 (2, N=771) = 3.208, p = .201, n.s.$ did not confirm a possible association between individuals with previous TBI and those who have been assessed with 'general intellectual loss' as selected from the interview summary section of the CAMDEX.

Hypothesis 8

TBI is a risk factor for changes in personality and impaired psychosocial function. A Pearson's Chi-square analysis of group differences explored the association of each group with marital status. The results of the analysis suggest that there is an association between group and marital status: $\chi^2 (6, N=777) = 17.43, p = .008$. Further, based on the expected values of the cross-tabulation by marital status, there were more seniors with TBI who had never married, fewer who had married, more who were separated and more who were divorced than expected in the sample (see Table 10). Further, when Pearson's Chi-square was completed to compare the association between the single item 'divorce' and group, significant results were also found: $\chi^2 (1, N=780) = 9.80, p = .002$.

Table 10

Marital Status for TBI and nonTBI Participants

Marital Status		Expected and Observed Counts		
		TBI	nonTBI	Total
Never Married	Count	36	62	98
	Expected	32	66	98
Married	Count	85	212	297
	Expected	99	198	297
Common-Law	Count	3	2	5
	Expected	2	3	5
Separated	Count	10	10	20
	Expected	7	13	20
Divorced*	Count	17	11	28
	Expected	9	19	28
Widowed	Count	109	220	329
	Expected	109	220	329
Missing	Count	0	3	3
	Expected	1	2	3
Total Count		260	520	780

* p = .002

Post Hoc Analysis

Two additional post hoc analyses were performed to explore the above findings in a more thorough manner. First, the living situation (institution vs. community) at CSHA-1 was explored. A Chi-square analysis using the Fisher's Exact Test indicated a significant association between residence type and seniors with TBI: $\chi^2 (1, N=780) = 5.71, p = .011$. For persons with a previous head injury, 41% lived in institutions at CSHA-1. In contrast, for persons with no previous head injury, 32% lived in institutions at CSHA-1.

Table 11

Residence of TBI and nonTBI Participants shown in Percentages

Living Situation at CSHA-1	TBI	nonTBI
Live in community	59	68
Live in extended care institutions	41	32

Additionally a one-tailed post hoc analysis was performed using Pearson's Chi-square to explore the possible effect of TBI on other psychosocial factors such as the living situation for those seniors residing in the community. Using the Community Questionnaire item 'do you live alone?', the possible relationship between group and this psychosocial variable was examined. The result suggested an association between the community living situation of participants and group: $\chi^2 (1, N = 491) = 3.04, p = .05$. Additionally, the number of persons with TBI who live alone was greater than expected and the number of persons with TBI who

do not live alone was lower than expected. For persons with a previous head injury living in the community at CSHA-1, 40% lived alone in community whereas 32% of those with no previous head injury lived alone.

Table 12

Living Situation for TBI and nonTBI Participants shown in Percentages

Living Situation at CSHA-1	TBI	nonTBI
Live alone in community? - Yes	40.1	31.9
- No	60.0	68.0

Mortality

Hypothesis 8

TBI may be a risk factor for early death. Chi-square analysis of group differences was performed to explore the association of group with a report of death from the Canadian Registrar of Vital Statistics. Chi-square analysis and Fisher's Exact Test indicated that report of death and TBI groups are independent of each other because the proportion of TBI and nonTBI in each remains the same. Therefore, no association between report of death and group was revealed: $\chi^2 (1, N=780) = .010, p = .490, n.s.$

Discussion

The purpose of the present study was to examine the cognitive outcomes of persons over 65 who had previously sustained a head injury with loss of consciousness. This research is among the first to explore cognitive decline in a sample of aging post-injury survivors. The primary aim was to test a number of a priori hypotheses suggesting that there is increased likelihood of cognitive and functional decline after a traumatic brain injury with age, and further, that previous traumatic brain injury may lead to dementia and early death. The rationale is that TBI and dementia affect similar neural structures or structures associated with similar functions of the brain. Therefore, persons with previous head injury would have less brain reserve and would subsequently experience more cognitive impairment as they age, than those without previous head injury. Comparisons to elderly people without head injury were used to address the influence of the TBI itself on outcome compared to expected changes with age. Additionally, the potential mediating effect of education was explored.

However, the results of this study are not conclusive; they do not allow us to make clear statements about the relationship between TBI and cognitive decline in elderly survivors of head injury. Yet, the findings do point to psychosocial impacts that previous head injury can have on the living situation and marital status of seniors.

Previous studies suggest that mortality and functional disability are higher in older persons than they are in younger persons following severe TBI, however the situation is less clear with how older persons with head injury compare on cognitive abilities to others their own age. It also remains unclear whether a previous TBI is a risk factor for cognitive decline and dementia, or if it accelerates pathological processes. The other studies have yielded

equivocal results. Differences in the methodology, the rigour of the studies, samples sizes, injury severities and the use of different measures of cognitive outcome may have contributed to inconsistencies in the published results. This study showed some weak trends in support of proposed hypotheses but few statistically significant differences were found between those with and without previous head injury.

Although an association between TBI and cognitive decline was not supported by these data, caution is advised in drawing conclusions and implications because methodological shortcomings and sampling difficulties may have confounded the results. This is a drawback of this prospective research. The following sections will analyse the issues inherent in the study and the significance of the findings, and make suggestions for future research.

Methodological issues

Group characteristics indicated that there was a near perfect match between the participants who reported having sustained a head injury and those that did not in terms of age, gender and years of schooling. Therefore, the method of matching participants with head injury to those without previous head injury on these key features appears successful. However, the reader is cautioned of methodological difficulties inherent in the study.

Of primary concern are the potential weaknesses in the method used for case selection and with it the strength of the TBI measure. The selection of persons with previous head injury was dependant upon a single, self-reported instance of head injury with loss of consciousness. There was no supporting clinical or anatomical confirmation. Therefore, neither an injury to neural structures nor the severity of the injury could be confirmed.

However, while self-reported head injury is not ideal, in that there are more reliable and valid measures of TBI, it is all that was available.

In order to "stage " the traumatic brain injury when a patient is admitted, most clinicians use the Glasgow Coma Scale (GCS) as a severity marker to determine the depth of coma (Stambrook, Moore, Lubusko, Peters & Blumenschein, 1993). However, use of GCS is not without difficulties because early GCS scores are frequently contaminated by alcohol or drug ingestion or other nonneurological trauma. As well, the usefulness of this measure is limited due to its restricted range; it does not rate mild injury very accurately. Therefore, the preferred clinical practice is to use the length of posttraumatic amnesia (PTA), or coma duration, as an additional identifier of injury severity (Rapport & Feinstein, 2000). These measures are also useful in predicting outcome after TBI.

Yet, GCS and PTA information were not available for this study and there were only three participants for whom coma duration had been documented in the variables contained in the CSHA database. Had this information been available, we would have greater confidence that the self-reported information was accurate and there would have been confirmation of injury to neural structures. Alternatively, radiological confirmation of lesion characteristics to estimate lesion size would have been useful since this is also an accepted and reliable method to verify the presence of injury and its severity (Ommaya & Gennarelli, 1974; Bostrom & Helander, 1986). Computerized Axial Tomographic (CT) scans were conducted for some participants of CSHA following their injuries, and so that information was available for a few people. However, it is expected that the regular use of 'state of the art' neuroimaging techniques like CT and magnetic resonance imaging (MRI) were not widely available or regularly employed during the time that many of these participants sustained their injuries.

Therefore, there was no clinical confirmation of self-reported head injury with loss of consciousness, no manner to gauge the severity of the injury, and no way to test the reliability of the self-report used to identify previous injury.

Had this information been available one could also more readily have determined the magnitude of the impact of TBI on cognitive functioning based on injury severity. One would anticipate finding a greater effect, and a statistically significant difference, in those with more severe injuries. There is no way of knowing if all severity levels of injury were represented in this study. If all levels were represented, most of the injuries would be of mild severity because mild injuries are more prevalent than severe. In Canada, approximately 50, 000 patients suffer a traumatic brain injury each year. Of these, 80% fall into the mild traumatic brain injury category (Johnson, 2001).

Another concern relates to healthcare databases. Prior research has suggested that the reporting of head injuries in healthcare databases is plagued with difficulties. The identification and reporting situation is now improving with the collection of some additional measures like PTA, length of coma, etc. However, there was a great deal of useful but missing information in provincial health care records particular to TBI during the time these data were collected (for a review of head injury and TBI reporting in BC Health services databases see Motier-Krentz, 1993). Even now, identifying TBI at the time of injury remains problematic as head injury is often complicated by other critical nonneurological organ system trauma sustained at the same time as the head injury. Alternately, the injury is often too 'mild' to be measured at the time of injury. This also has a negative effect on the reporting of traumatic brain injury, in that it is often under reported and therefore the healthcare databases are not

complete (Motier-Krentz, 1993). As a result, for the purpose of the CSHA data and this study, information from self-reported injuries was the best that was available.

Finally, measuring outcome after TBI remains a difficult task. Of particular difficulty are studies of long-term cognitive outcomes after TBI. While cognitive impairment is an important factor in the outcome of younger patients, this may have particular significance in an elderly population that is at increased risk for cognitive dysfunction to begin with. Prospective outcome studies after TBI are costly and methodologically difficult. There are many confounding effects of aging and chronic illness on cognitive ability that are difficult to control for, as well as other possible influences on cognitive function associated with having sustained a TBI. For example, post-injury medication use, depression (Brown, Scott, Bench & Dolan, 1994) and post-injury substance use/abuse (Corrigan, 1995) can have negative effects on cognitive ability. As such, long-term outcome studies of aging head injury survivors fall beyond the scope of most research.

Further, studies involving seniors and TBI have focused on the immediate and post-acute recovery phase rather than the very long-term outcome, that is, into old age. No other studies have explored the increased likelihood of the survivor experiencing CIND as they get older, as a consequence of previous head injury. Yet this is an area worthy of further study because research has shown that 50% of those diagnosed with CIND progress to a diagnosis of dementia within 5 years (Tuokko et al., 1991).

Diagnosis of dementia and diagnosis of cognitive impairment not dementia (CIND)

The results of this study suggest that there is a negligible difference (< 2.0 %) between those with and without head injury in the sample of participants who were diagnosed with

dementia at CSHA-1. Then, five years later, at CSHA-2, 3.0% more people with *no* previous head injury were diagnosed with dementia compared to those participants with previous head injury. However, this was a nonsignificant association and is in keeping with CSHA research that also did not find head injury with loss of consciousness to be a risk factor for dementia (CSHA, 1994). Further, previous research showed that head injury achieved only borderline significance as a risk factor for Alzheimer's disease (CSHA, 1994). However, these results may reflect weaknesses in the case selection of head injury.

There is no previous research that explores the relationship between CIND and TBI. This study also found a negligible difference in the likelihood that people with head injury will develop CIND. One percent more of those with reported head injury were diagnosed with CIND at CSHA-1 than those without head injury. Five years later, at CSHA-2, 2.0% more with head injury were diagnosed with CIND than those without. This study adds to the current research on CIND in that it is the first to explore the relationship between head injury and preclinical cognitive decline.

Post hoc analyses

Quantitative analysis revealed a pattern of differences between expected and counted diagnoses for those with a previous history of head injury. As such, the cognitive state of those with reported head injury was explored in a more meaningful way using another variable from the original CSHA database. This information combined the diagnosis of dementia at CSHA-1 with residence information and reported death. This analysis revealed that although there was no difference between the number of survivors diagnosed with dementia or CIND, there existed a negative trend in living situation related to the diagnosis of

dementia. Specifically, 6.2% more people with a history of head injury were living in institutions at CSHA-1 *without having dementia* as compared to people with no history of head injury that live in institutions but do not have dementia. One could assume that those with previous head injury are living in nursing homes and chronic care facilities primarily to allow for the management of medical, behavioural and physical sequelae, some of which may have been the result of their head injury. Or it may reflect differences in the marital status of TBI survivors, in that single people may be more likely to live in institutions than those who are married and living with their spouses. Alternately, it may be that there simply not enough alternate residential care beds for TBI survivors. A previous review of the utilisation of extended care beds discovered that there are younger adult TBI survivors placed in extended care facilities for the aged (Motier-Krentz, 1993). Therefore, it is possible that some adult TBI survivors simply remain in seniors facilities until they become seniors themselves, for lack of a more appropriate placement. The finding of more TBI survivors without dementia in institutional care brings to question the appropriateness of TBI survivors being placed in seniors' facilities given both the prevalence of TBI, and the number of other aging people that will require care. Will we have enough resources and if not, who should have access? Any attempt to answer these questions moves beyond the scope of the present study. Yet, this point is important and should be addressed in future studies of healthcare service utilisation by those with TBI.

Neuroprotective effect of education

To explore whether education can act as a form of cognitive reserve and thus reduce the likelihood of cognitive decline, the relationship between years of education, diagnosis of

dementia, intellectual decline and death was explored. However, there were no significant associations between education and head injury and receiving a diagnosis of dementia, experiencing intellectual decline, or death. However, this study is the first to explore the relationship between education and cognitive decline in older head injury survivors and more research is needed in this area before statements can be made with confidence about this relationship.

Earlier diagnosis of cognitive decline

There was also no compelling evidence that head injury is a risk factor for earlier cognitive decline leading to earlier diagnosis of dementia or CIND. At CSHA-1, on average, those with previous head injury were less than six months younger when they received a diagnosis indicative of cognitive decline than those without previous injury. Five years later, those with prior head injury that were *newly* diagnosed with dementia or CIND were on average, one year younger than those without head injury. However this was not a statistically significant difference. This finding adds to existing research in that it may be the first study to explore the relationship between earlier CIND and TBI in an elderly population. More research is required before we will know if, over time, those with head injury may be at increased risk for cognitive decline. Further, this study improves upon earlier research that failed to carefully screen out those with previous cognitive impairment in that only new instances of CIND and dementia were counted at CSHA-2.

Reduced memory

As would be expected, scores on memory measures by participants in both groups declined significantly over the five year period between CSHA-1 and CSHA-2. However, overall, of those for whom memory abilities were tested, those with previous head injury did not have lower scores at either the beginning or after five years. Instead, the pattern of decline showed that those in the TBI group scored slightly higher on some measures at CSHA-1 and then had a larger drop in scores at CSHA-2. Yet, the significance of this change in scores may be negligible. Further, it may be that the pattern of memory decline is nonlinear or that a five year interval between testing sessions was not long enough to see a difference in the two groups.

The difference between the memory abilities of people in the two groups overall were not sufficient to withstand up to the rigor of omnibus testing. However, univariate tests conducted during this study suggested that the Weschler Memory Scale Information subtest scores (WMS) and the Buschke total cued and free-recall scores (Buschke) show promise for detecting a difference in the memory abilities of those with and without head injury after five years. The WMS Information subtest is a measure of semantic memory. Those with head injury scored higher the first time they were tested but then scores declined further than those without head injury when tested again five years later. This suggests greater variability in semantic memory in those with previous head injury when compared to those without head injury who showed less change in function when tested five years later. The results are in keeping with those of Tierney (2005) who reported that WMS Information subtest scores predicted Alzheimer's disease after 5 years. The predictive validity of these scores in those with previous head injury has not been explored.

The Buschke total delayed score is a measure of delayed word recall. Cues are given to reduce the cognitive effort required and therefore separate memory ability from the effects associated with normal aging. The retention and retrieval scores of the Buschke have reliably predicted dementia 62% of the time (Tuokko et al., 1991). Again, those with head injury scored higher the first time they were tested but then their scores declined more than those without head injury who showed less decrease in function five years later.

The ability of these measures to detect a difference between those with and without head injury is in keeping with previous research that has suggested that differences in episodic memory could be identified five years prior to diagnosis of dementia (Masur, Sliwinsky et al., 1994). It is encouraging that it appears these measures can differentiate between those with and without head injury. However, it remains questionable whether the small changes in mean scores on these measures are clinically meaningful or are just spurious findings.

Methodological issues, revisited

There is a possibility that the researcher was too conservative during the analysis of the memory measures. The analysis required a significant omnibus test across all the memory measure scores detecting a difference between those with and without head injury. Since significant results were required prior to consideration of the differences between individual memory measures, this may have inflated the possibility of a Type II error. As such, the requirement may have critically decreased the statistical power to detect a difference between the two groups. Further, the requirement reduced the opportunity to explore the differences in specific memory functions of those with and without head injury.

Although the sample size was deemed adequate for the analyses, it is possible that the effect size was too small given the sample. The effect size in the sample may have been reduced because those with very severe cognitive impairment were not given memory tests, having been excluded from the neuropsychological testing by way of their scores on the 3MS. The CSHA procedure did not involve neuropsychological assessment for any participants who screened below 50 on the 3MS; rather, it just sampled those that scored between 50 and 78. Consequently, the spectrum of impairment captured by those given memory tests in this study likely represents those of mild to moderate severity. Therefore, although the results suggested that head injury had no effect on memory, this analysis did not include those with the most severe injuries, thus selection effects may have influenced the results.

Additionally, the tests originally chosen for CSHA were originally selected due to their ability to detect dementia, not for their ability to identify cognitive decline prior to clinical detection of dementia. Subsequently, ceiling effects likely occurred because most people received near perfect scores. Finally, it was anticipated that the scores of the neuropsychological measures used in this study would be indicative of injury severity. However, the measures may have lacked the sensitivity to identify the TBI effect on cognitive decline. It can not be determined if our inability to detect differences in memory functions is the result of ceiling effects, or insufficient sensitivity of the memory measures or the lack of a measurable effect of previous head injury on cognitive functioning in this sample.

General intellectual decline with input from family

Previous head injury may be a risk factor for general intellectual decline beyond that associated with normal aging, but the association is not clear. Over a five year period slightly

more TBI than expected were assessed as having greater general intellectual decline on ratings of interviewer summaries. However, the results did not suggest that those with head injury had greater intellectual loss than other aging people.

Changes in personality and impaired psychosocial functioning

A previous study reported the primary source of concern reported by families of TBI survivors are the long-term emotional and social sequelae of traumatic brain injury including change of personality (Dawson & Chipman, 1995). Likewise, in the current study, the most robust difference between those with and without previous head injury was related to psychosocial issues. Those with previous head injury were more likely to have never married (14%) or to be divorced or separated from their spouse (10%). These findings support previous research that showed spousal relationships following brain injury are particularly vulnerable to strain and breakdown (Boswell, McErlean & Verdile, 2002; for a review see Perlesz, Kinsella & Crowe, 1999) and that people with TBI may never marry. For example, a 20 year follow-up study with TBI survivors of all severities revealed that significantly less brain injured people were married and the prevalence of divorce among them was 11.8%, which was higher than the national rate. Of note, 5% of these divorces occurred post-injury (Hoofien, Gilboa, Vakil, & Donovick, 2001). Also, when Thomsen (1992) interviewed thirty one patients with severe TBI 20 years post-injury, only four were married. Further, when Dawson and Chipman explored the marital status of community living survivors at an average of 13 years post-injury, they reported a 34% marriage rate and that 47% of the survivors had never been married (1995).

The current finding that older people with previous head injury are often still single or are divorced suggests that the potential for negative effects of TBI on personality and family functioning persist throughout the lifespan. Rothweiler et al. also reported increasing levels of psychosocial limitations are associated with persons with TBI 60 years and older (1998).

A review of the marital status of those with previous head trauma in this study suggested that their injuries may have contributed to their decreased ability to maintain familial relationships. However, it is also possible that other factors such as premorbid personality may have also contributed to any difficulties in family functioning. Further, it is possible that some of the head injuries occurred after the person was divorced or separated. Regardless, the finding suggests a need for more intense and longer clinical interventions to identify and address these difficulties and for further research, because TBI survivors may be particularly vulnerable to the psychosocial impact of TBI as they age.

Post hoc analysis 1

Quantitative analysis revealed a pattern of differences between expected and counted living situations for those with a previous history of head injury. As such, the living situation of those with reported head injury was explored in a more meaningful way using another variable from the original CSHA database. This analysis indicated that at CSHA-1, 9% more people with previous head injury were living in institutions than those with no previous head injury and this difference was significant. Marital status and whether or not a person lives alone are likely highly correlated. This finding suggests that service utilisation by head injury survivors is an area worthy of further investigation and raises concerns about long-term outcomes and the quality of life for head injury survivors. The finding may indicate that

increased support for caregivers and families may be warranted so that survivors can continue to live in the community.

Post hoc analysis 2

A second post hoc analysis was conducted to explore the living situation of those with previous head injury in a more thorough manner using another variable from the CSHA database. This qualitative analysis suggested that, for those with previous head injury, living in the community was not necessarily associated with a better outcome. A trend was revealed wherein 8.0% more people with previous head injury lived alone at CSHA-1 than those without previous head injury. While this amount is not large, given the sample size this finding has implications for the quality of life of head injury survivors and suggests that this group may be at increased risk for social isolation with age. When questioned, TBI survivors in Dawson and Chapman's previous study reported the lack of social contacts as their primary source of concern (1995). This finding was corroborated by Thomsen during a 20 year follow-up of those with severe TBI wherein she discovered that about half the head injured participants lived alone (1992). She also reported that 61% of her patients had no contact with friends or acquaintances other than family. Hoofien, Gilboa, Vakil & Donovan (2001) also conducted 20 year follow-up study that explored social functioning. This group found 8% of community living survivors of mixed injury severity reported having no social support at all, in that, the survivors were living in the community in complete social isolation. These findings suggest a need for more research in this area to explore and monitor more closely the long-term outcomes for head injury survivors. In this way key interventions can be identified and supports utilised to maintain quality of life for survivors as they age.

Increased likelihood of death

There was no evidence in this study that previous head injury increases the risk of death. This is generally in keeping with one study that reported that the average life expectancy of persons with severe TBI is 50 years post-injury (Chamberlain, 1995) in that, assuming the TBI survivors acquired their head injury during the most common age period, 25-45, they are still alive at the time of CSHA, at 65 years plus. There is previous evidence that more, older victims of TBI succumb to their injuries during the acute medical phase than those younger and also some evidence that there is higher mortality nine years post-injury. However, this study suggested that there is no increased risk of death in seniors with previous head injury. However, the ability to find a difference in mortality might have been strengthened by the analysis of the number of persons who died after CSHA-2 (i.e. as collected during CSHA-3). That analysis may show a difference since the participants are another 5 years older.

Future Studies

Prospective longitudinal studies are called for that carefully document the clinical course of cognitive decline in aging brain injury survivors. Information regarding the severity of the head injury, demographic, and medical variables, as well as the existence of pre-morbid cognitive dysfunction or pre-morbid ability, would be ideal. Measures of pre-morbid ability in particular have been overlooked in the majority of studies to date. Cognitive impairment after TBI is an important factor during rehabilitation. However, this may have particular significance in an elderly population that is at increased risk for cognitive dysfunction to begin with. Memory measures with established validity and preferably, age-based norms

could be utilised and could include those measures that are more resistant to ceiling effects and more sensitive to mild cognitive impairment. Future studies should also explore psychosocial impairment, family functioning and living situation of aging brain injury survivors.

During the CSHA, data were collected at 5-year intervals: CSHA-1 in 1991, CSHA-2 in 1996, and CSHA-3 in 2001. CSHA-3 was designed to estimate the prevalence and risk of progression from various categories of cognitive impairment or loss to dementia, based on the classification developed at CSHA-2. There are two main reasons that having CSHA-3 data available would improve the results of this study. To utilise the CSHA-3 data from the same participants after another 5 years would add depth to our understanding of the impact of head injury on age by allowing for the exploration of a possible nonlinear relationship between TBI and cognitive decline. Also by following the group of seniors for another 5 years, a ceiling effect would be reduced because both groups are older and presumably more cognitively impaired. In so doing, we may detect if those with previous head injury age differently from those with no previous head injury in hopes of identifying head injury as a risk factor for later cognitive decline.

Conclusion

It would be premature to conclude from the published studies or this research that the elderly have a uniformly poor cognitive and functional outcome following TBI or, that TBI increases the risk of cognitive impairment and dementia with age. However, if it does, the cumulative effect of high prevalence of TBI and our expanding demographic of seniors could have a tremendous impact on the quality of life of survivors and their families and overwhelm

our already overburdened healthcare services. The author concludes that further exploration of cognitive decline and dementia in aging survivors of head injury is worthy of further research. Given the shifts in demographic balance with increasing numbers of elderly patients living longer, the effects of TBI in the population deserve serious and concerted study.

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