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DEMENTIA (KS MARDER, SECTION EDITOR)

Update on TBI and Cognitive Impairment in Military Veterans

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Abstract Traumatic brain injury (TBI) is a common cause of morbidity and mortality in military life. Interest in military TBI has increased recently due to the conflicts in Iraq and Afghanistan. Certain types of TBI are relatively unique to the military, the most prominent being blast-related TBI. Blast-related mild TBI has been of particular concern in veterans from the most recent conflicts although controversy remains concerning its separation from post-traumatic stress disorder. TBI is also a risk factor for the later development of neurodegenerative diseases in which cognitive impairment is prominent putting veterans at risk for disorders including Alzheimer's disease and chronic traumatic encephalopathy. Recent evidence associating TBI with chronic cognitive impairment is reviewed in the context of its relevance to military veterans.

Keywords Alzheimer's disease · Blast · Chronic traumatic encephalopathy · Dementia · Traumatic brain injury · Military veterans

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Introduction

Traumatic brain injury (TBI) is an unfortunately common event in civilian and military life. Worldwide TBI incidence likely approaches 10 million cases per year [1]; although because many cases of mild TBI (mTBI) go unreported, true global incidence of mTBI probably approaches 42 million per year [2]. Certain populations such as athletes engaged in contact sports and military personnel are particularly prone to TBI with TBI being a major cause of combat related disability [3] as well as health care costs to the Department of Veterans Affairs (VA) [4].

Indeed TBI is of long standing interest in military medicine. DePalma [5] notes that Homer's *The Iliad* written about 800 BCE describes the first casualty of the Trojan war as a combat head injury inflicted upon the warrior Echepolus. Accounts of the Trojan War also describe the mental and behavioral sequela that may follow head injury. By the time of the American Civil War (1861–1865), the seriousness of closed head injuries were well appreciated [6]. During the 20th century major advances occurred in surgical and rehabilitative care of military TBI [7]. From 2000–2014, over 320,000 US service members sustained TBIs worldwide [8], with public awareness of TBI in military medicine increasing recently due to its frequency in the conflicts in Iraq and Afghanistan [9].

Acutely, TBI may be associated with transient or permanent cognitive deficits [10]. There is mounting evidence that moderate to severe TBI is a risk factor for the later development of neurodegenerative diseases in which cognitive impairment is prominent [11]. Repetitive mTBI has been associated with the entity now known as chronic traumatic encephalopathy (CTE) [12]. Because of its frequency in military veterans, the relationship of TBI to acute and chronic cognitive impairment is an issue of concern. Here, recent evidence associating TBI with in particular chronic cognitive

impairment is reviewed in the context of its relevance to military veterans.

Traumatic Brain Injury in the Recent Conflicts in Iraq and Afghanistan

As of 30 June 2012, over 1.5 million Iraq and Afghanistan veterans had left active duty [5] with estimates that 10–20 % of these veterans suffered a TBI during deployment [13, 14]. Initially, most attention focused on those with moderate to severe TBI, the type of injury that would be recognized in theater and the war in Iraq has lead to the highest number of service related severe TBIs since the war in Vietnam [15]. However, many returning veterans began appearing at VA medical centers with symptoms suggestive of the effects of mTBIs that had not been recognized in service. Indeed estimates are that between January 2003 and October 2006 over 80 % of TBIs suffered by U.S. troops deployed in Iraq or Afghanistan went undocumented [16•].

To address missed cases, the Department of Defense (DoD) and VA initiated measures to increase diagnosis. In 2007, DoD implemented TBI screening in the field [17], as soon as practical soldiers are evaluated by medics using a structured assessment tool known as the Military Acute Concussion Evaluation (MACE). The revised version of the MACE which has been in use since 2012 [18] includes historical questions concerning the mechanism of injury (e.g., blast, fall, motor vehicle accident), if a helmet was worn and whether there was loss of consciousness or amnesia surrounding the event. The brief examination assesses the cognitive domains of orientation, immediate memory, concentration, and delayed recall as well as records a neurological exam that includes assessments of eye tracking, speech, motor strength, and balance. Maximal score on the exam is 30. Scores below 25 are considered suggestive of the need for further evaluation although the MACE has never been fully validated and appears to have little utility if administered more than 12 h after the incident [19].

After May 2008, to provide a baseline against which cognitive functioning post-injury could be compared, the DoD instituted baseline neurocognitive testing prior to deployment using a 15-min computerized assessment tool known as the Automated Neuropsychological Assessment Metrics (ANAM; [20]). The ANAM includes tests of code substitution, procedural reaction time, matching to sample and mathematical processing. The ANAM appears to have clinical utility if administered within 72 h of injury [21] and the reaction time based subsets of the ANAM4 battery may have some longer prognostic utility [22].

To capture missed cases in returning veterans, the VA mandated TBI screening of all Iraq and Afghanistan veterans presenting to VA hospitals for any reason using a four-question screening tool [23–25]. The VA established a nationwide Polytrauma/TBI system of care to deal with positive screens and other identified cases [24, 25, 26]. By 31 July 2013, more than 760,000 veterans reporting to VA facilities had received mandated TBI screening resulting in over 150,000 positive screens which lead to specialized evaluations at Polytrauma/TBI clinics [5].

Differences Between Civilian and Military TBI: The Role of Blast

As in civilian life, military-related TBIs occur through a variety of mechanisms including vehicular crashes, falls and injuries sustained in sports or other recreational activities as well as military training. Indeed, the DoD estimates that 80 % of TBIs suffered by active duty personnel occur in non-deployed settings suggesting that most military-related TBI occurs through mechanisms similar to those encountered in civilian settings [5]. By contrast certain types of TBI are relatively unique to the military, the most prominent being blast-related TBI. In civilian life, blast injury is an uncommon cause of TBI. A survey of over 57,000 trauma cases in an urban trauma center found that only 0.2 % involved blast [27]. By contrast in the conflicts in Iraq and Afghanistan, because of the wide spread use of improvised explosive devices (IED), blast-related mechanisms have been the most common cause of TBI [13, 14].

In the type of blunt impact injury, typical of civilian TBI rotational and inertial forces combine with the local effects of blunt trauma to cause tissue damage [28, 29]. By contrast blast injury results from a pressure wave transmitted though air from a distance. Damage to the nervous system is thought to occur through interactions between the traveling pressure wave and the brain itself [30].

Because of its distinctive character, questions have emerged as to whether the underlying pathobiology of blast-related TBI is different from non-blast. In humans, high-pressure blast waves can cause extensive injury. High-level blast waves also cause extensive pathology in animals that includes a prominent hemorrhagic component as well as a variety of axonal and other pathologies [17, 31, 32]. Blast injuries this severe are without doubt a mix of injury mechanisms that overlap with those found in non-blast TBI. Less clear is how damaging the primary blast wave is in the context of blast-related mTBI. Low-pressure blast waves are transmitted to brain [33•]. In animals, they have been associated with various effects [33•]. Human neuroimaging studies document that blast-related mTBI can be associated with chronic effects the most consistent being reduced fractional anisotrophy (FA) on diffusion tensor imaging (DTI) [33•]. Yet because of the difficulty of distinguishing blast-related mTBI from post-traumatic stress disorder (PTSD), controversy exists

concerning the role of blast-related mTBI in the production of chronic symptoms.

Controversies in the Diagnosis of Blast-Related mTBI

Mental health problems are common after TBI [34]. A striking feature of the mTBI being seen in the most recent veterans is the concurrent presence of PTSD [17]. Indeed over one-third of Iraq veterans suspected of having an mTBI-related postconcussion syndrome also have PTSD or depression [13, 35]. The presence of PTSD complicates diagnosis, since clinically, distinction between the two disorders is often difficult due to their overlapping symptoms [17].

MTBI and PTSD might be associated due to independent exposures to TBI events and PTSD stressors. However, others have suggested that the apparent epidemic of mTBI in Iraq and Afghanistan veterans may be an artifact of how mTBI is currently defined and the lowering of the threshold for making an mTBI diagnosis to the most transient alterations of consciousness (reviewed in [33•]). Multiple studies have suggested that postconcussion symptoms following blast-related mTBI may be better explained by PTSD or related to blast only when the TBI involves loss of consciousness which describes the minority of cases in Iraq and Afghanistan veterans. Indeed, a 2014 report on the long-term consequences of blast from the Institute of Medicine [36] concluded that based on human studies there is "limited/suggestive evidence that most of the shared symptoms are accounted for by PTSD and not a direct result of TBI alone." For postconcussion symptoms and persistent headaches following blast-related mTBI, the report concluded that sufficient evidence only existed to suggest an association.

The controversy of psychological vs. physical injury itself is not new dating back to the entity of "shell shock", a term coined during World War I when it was first recognized that symptoms reminiscent of what might now be called a postconcussion syndrome or PTSD could follow blast exposure [37]. TBI and PTSD have an interesting relationship in that they can be viewed as different ends of a spectrum with TBI being an organic brain disease. By contrast, PTSD is conceptualized as being rooted in a psychologically based reaction to a stressor that did not produce physical injury. The distinction is of more than academic interest as it impacts treatment approaches as well as patient education [17]. Therapies for PTSD typically focus on normalizing stress reactions through psychologically and pharmacologically based treatments. By contrast, TBI treatments are based on an organic model which assumes existence of structural brain alterations with recovery dependent on resolution of these neurological factors.

Other studies suggest that links between mTBI and PTSD may not be coincidental. For example, in Vietnam veterans TBI is associated with more severe PTSD [38] and studies from veterans of the most recent conflicts suggest the development or worsening of PTSD following blast-related mTBI [39]. When blast-related mTBI in humans has been studied by neuroimaging, chronic decreases in fractional anisotrophy have been observed which are suggestive of axonal injury and unlikely to be explained by co-morbid PTSD [33•]. In animals, low-level blast exposures that cause little CNS pathology nevertheless induce PTSD-related behavioral traits without a psychological stressor as well as render animals more sensitive to PTSD-related stressors [33•]. In some studies, these traits were present many months after blast exposure suggesting that blast-related behavioral changes may be long lasting [40•]. Thus, while one body of studies suggest that much of what is presently being called postconcussion syndrome secondary to blast-related mTBI is really PTSD, other evidence suggests that low-level blast exposure may induce PTSD-related traits without the need for a psychological stressor. Interestingly, one recent study found that 45 % of those seeking treatment at a VA mental health facility had suffered a probable TBI suggesting that the role of TBI in mental health settings may be underappreciated [41•].

Traumatic Brain Injury and the Risk for Later Dementia

Memory impairment is common following TBI [10]. Post-traumatic amnesia is one of the features used to define TBI severity. A general relationship exists between TBI severity and cognitive effects with longer durations of impaired consciousness associated with greater and more persistent cognitive impairment. Mild cognitive complaints are common as part of a postconcussion syndrome following an mTBI but generally resolve within 6 months. Chronic cognitive complaints are seen in a subgroup of patients with mTBI more often in those in whom neuroimaging reveals focal intracranial lesions. Recovery among military veterans after mTBI is also the rule although one recent study found that most continued to have somatic complaints such as headaches or mental health problems 5 years after the event [42]. Moderate to severe TBI is associated with more severe and persistent cognitive deficits. Improvement usually plateaus by 24 months with as many as two-thirds of moderate to severe TBIs left with long-term cognitive deficits and nearly a quarter failing to return to work in the year following injury [10]. A study of predominately Iraq or Afghanistan veterans who suffered moderate to severe TBIs found that about half remained symptomatic in some form 3 years after injury [43].

Thus, static cognitive impairments following especially moderate to severe TBI are well recognized. More recently,

it has become recognized that TBI is a risk factor for later development of dementia [44]. In veteran populations, Barnes et al. [45] found that in older veterans any TBI was associated with a 60 % increase in the risk of developing dementia over a 9-year period. A prospective study of World War II veterans found a two to fourfold increase in the hazard ratio for developing dementia in older veterans with a history of a moderate to severe TBI suffered 50 years earlier [46]. Systematic reviews have concluded that a history of at least one moderate to severe TBI increases the odds ratio for developing dementia compared with individuals with no TBI history [47, 48].

Risk for dementia after mTBI is less conclusive. Previous systematic reviews and an Institute of Medicine report concluded that there is no increased risk for dementia later in life after an mTBI without loss of consciousness [47, 48]. One study also found no increased risk for dementia in World War II veterans with a history of mTBI [46]. However, repetitive mTBI has been associated with the entity now known as CTE [12], and one study recently suggested that mTBI may be a risk factor for developing dementia if the TBI occurs after age 65 [49].

Dementia following TBI is best recognized following the type of blunt force trauma typical of civilian TBI. Whether blast exposure is a risk factor for the later development of neurodegenerative diseases is unknown. Indeed, little is known about long-term outcomes following blast-related mTBI. One study of 167 U.S. military service personnel evaluated within 5 years of sustaining an mTBI during operations in Iraq and Afghanistan found that although many improved, ≈20 % reported new symptoms [50]. It is currently unknown if blast injury is capable of initiating a chronic neurodegenerative process although a study in rats examining diffusion tensor imaging (DTI) after a blast injury observed region-specific decreases in fractional anisotropy that expanded over a 4 to 30 day period [51•]. Whether these findings can be extrapolated to humans is unknown.

Chronic Traumatic Encephalopathy

An association between repetitive mTBI and chronic progressive neurologic dysfunction in boxers was first reported by Martland in 1928 [52], a condition which he referred to as the "punch drunk" or "slug nutty" syndrome. Similar cases were described by others and the syndrome later became known as dementia pugilistica [12]. Autopsy studies in the 1960s and 70s described the syndrome's neuropathology which came to be called CTE [53]. Omalu described CTE in a professional American football player in 2005 [54]. More recently, CTE has been reported in other sports including hockey, soccer, and professional wrestling [12, 55, 56].

CTE is a progressive neurodegenerative disease that typically presents following a latent period of years to decades after exposure to the repetitive trauma [12]. Subtle behavioral changes including alterations in mood or personality along with apathy, poor impulse control, or aggression are typical presenting features. Initially, cognitive impairment is usually less apparent than the behavioral component. Disease begins insidiously but is followed by a slow progressive deterioration. Neuropsychological testing most consistently reveals deficits in memory and executive function. Later stages may be characterized by frank dementia although in some series of neuropathologically confirmed CTE, dementia has been present in only a minority [56]. Mostly later in the disease, CTE may be associated with Parkinsonian features or motor neuron disease [12, 57•]. As in AD, apolipoprotein E genotype appears to play a role in CTE susceptibility and other genetic risk factors seem likely [12].

Pathologically, CTE is primarily a tauopathy with aggregates of phosphorylated tau deposited as neurofibrillary tangles (NFT) in neurons and astrocytes [12]. The NFTs of CTE resemble those of AD but differ in their distribution with the neuronal and astrocytic aggregates of phosphorylated tau in CTE being found more in the superficial cortical layers, especially in the depths of the sulci [56, 57•]. In CTE, there is also prominent perivascular deposition of tau. While diffuse amyloid plaques may occur, CTE typically lacks the neuritic plaques characteristic of AD. In the cases reviewed by McKee [56], diffuse Aβ deposits were seen in 47 % of cases, while AD-like neuritic plaques were present in 27 %.

There might be particular concern for CTE in recent veterans because of the frequency of repetitive mTBI in Iraq and Afghanistan. Omula et al. [58•] first reported a case of CTE in an Iraqi war veteran with PTSD who committed suicide. This 27-year-old Marine was deployed twice to Iraq where he experienced repetitive blast exposures although no associated TBIs were documented. After his deployment, he suffered an mTBI while playing football and was in a motor vehicle accident. Following his second deployment, he developed a progressive cognitive and behavioral syndrome and was diagnosed with PTSD. At autopsy, his brain showed neocortical and subcortical NFTs in a multifocal pattern characteristic of CTE.

Goldstein et al. [59•] studied brains from four Iraq and Afghanistan veterans who were exposed to blast or concussive injury. Cognitive decline in combination with neuropsychiatric features including depression or behavioral changes were described in three of the four. Two of these three were diagnosed with PTSD, one of whom died from a self-inflicted gunshot wound and the other from aspiration pneumonia following ingestion of prescription analgesics. A fourth case was described as having headaches, irritability, and depression as well as difficulties with sleep and concentration that continued until his death from a ruptured basilar aneurysm 2 years after

initial symptoms developed. This last patient's only history of TBI was a single close-range exposure to an IED explosion that was associated with a 30-min period of disorientation without loss of consciousness. In all cases, there was perivascular and deep sulcal accumulations of tau in neurons and glial cells as well as dystrophic axons consistent with CTE. In the largest modern autopsy series of CTE, which included the four cases reported by Goldstein [59•], McKee et al. [57•] identified 21 military veterans among 85 cases. Sixteen of the twenty-one veterans were also athletes including eight National Football League players. Three had suffered a moderate to severe TBI, and three had been exposed to blast.

The risk of CTE among veterans is unknown. Indeed, the true prevalence of CTE in the general population is uncertain. Attempts to estimate prevalence are limited by the lack of consensus clinical criteria for CTE which is at present a neuropathological diagnosis. There may also be considerable overlap of CTE with other disorders. In the 68 cases reviewed by McKee et al. [57•], CTE was the sole diagnosis in only 63 % with other diagnoses including Alzheimer's disease (AD), Lewy body disease, frontotemporal lobar degeneration, and motor neuron disease suggesting that other neurodegenerative disorders are frequently present. Whether blast exposure forms a unique risk for military combat veterans from the most recent conflicts is unclear. Studies in animals show that blast induces multiple aberrantly phosphorylated and cleaved-tau species acutely that are still present 30 days later [33•, 59•, 60]. Yet, few cases of CTE in veterans have been reported and most of these cases have included non-blast exposure.

Alzheimer's Disease

AD is the most common cause of senile dementia in the USA and Europe, a problem that will confront the aging veteran population as well [61]. Veitch et al. [62] have estimated that there will be 423,000 new cases of AD in veterans by 2020, including an excess of 140,000 cases estimated to be related to military exposure. The reason for this excess among military veterans is probably multifactorial, but TBI is likely one factor [44, 62].

Multiple studies support a link between single moderate-severe TBI and the later development of AD [46, 47, 63]. A meta-analysis of 15 case control studies found that in males a single TBI associated with loss of consciousness was associated with a 50 % increased risk of AD [63], and other studies suggest that TBI is associated with an earlier age of onset [64]. Similar trends are seen in military veterans. A study of World War II veterans found that those with severe TBI were four times more likely to have AD while risk was increased two-fold in veterans with moderate TBI [46]. This same study [46] found no association of mTBI with an increased risk of AD.

Speculation as to why TBI might be associated with an increased risk for AD has largely centered on the observation that proteins associated with AD accumulate in brain following TBI. The β-amyloid (Aβ) peptide deposits in the plaque amyloid found in AD. The longer Aβ 42 species can be neurotoxic and associated with a chain of pathological events that are thought to cause AD [65]. Aβ and its precursor the amyloid precursor protein (APP) protein also accumulate following TBI [66]. Indeed, changes in Aβ occur rapidly after TBI in humans. Diffuse cortical plaques and increased levels of soluble Aβ appear within 2 h of a severe TBI [11]. Aβ is also consistently elevated in experimental animal models of TBI [67] along with the β-site APP cleaving enzyme 1 (BACE 1), the principal β-secretase and components of the γ-secretase complex, both of which process APP toward the Aβ pathway [67]. As in AD, this process in TBI is likely affected by genetic risk factors such as apolipoprotein E genotype [68]. These observations suggest that TBI may initiate or accelerate a pathological shift in Aβ production, which is now known to begin decades before the onset of symptoms in AD unassociated with TBI. As in CTE, accumulation of tau also occurs in the NFTs found in AD.

AD is of increasing concern within the VA because of the aging veteran population. Also of concern is the future risk of younger veterans returning from the recent conflicts in Iraq and Afghanistan where blast-related TBI has been common. While this future risk is unknown, the single study that has examined Aβ levels following blast exposure in animals found that in rats and mice, rather than increasing, brain Aβ levels decreased acutely following blast injury [69•]. Unlike animal models of non-blast TBI, BACE-1 and the γ-secretase component presenilin-1 were also unchanged following blast exposure in rats [69•]. Axonal accumulation of APP which is regarded as a hallmark of acute axonal injury in non-blast TBI [70] also appears to be an inconsistent feature of blast-related TBI in animals [69•].

The unexpected lowering of Aβ by blast again raises the question of whether blast-related TBI is pathophysiologically distinct from non-blast TBI. While evidence on this subject remains limited one recent study comparing RNA changes between a closed head injury model and a blast TBI model suggested differences as well [71•]. In this study, while a common set of RNAs were elevated or depressed following either injury, most changes between the models differed suggesting that at the molecular level the injuries are distinct. A functional pathway analysis further showed that genes up regulated or down regulated in AD moved in similar directions following non-blast TBI injury while the opposite occurred after blast with "AD up" genes down regulated and "AD down" genes up regulated [71•]. Combined with the Aβ lowering effects of blast, these studies suggest that blast-related TBI may exert distinct effects on AD related pathways.

Other Neurodegenerative Diseases Associated with Cognitive Impairment

Besides Aβ and tau, other proteins associated with neurodegenerative diseases accumulate after TBI including α-synuclein, ubiquitin and neurofilaments [66]. Accumulation of these proteins occurs in disorders including Parkinson's disease and amyotrophic lateral sclerosis (ALS), which include an element of cognitive decline. Support exists for a link between single moderate-severe TBI and Parkinson's disease (PD) [47, 72] as well as amyotrophic lateral sclerosis (ALS) [73, 74]. Trauma has also been suggested as a trigger for ALS with evidence that TBI confers a more than a threefold increased risk of developing ALS within 10 years of injury [73–75]. Older age at the time of TBI also appears to reduce the latency between injury and ALS diagnosis [74].

Parkinson's disease is a common disorder in veterans. An association between ALS and military service was first suggested by epidemiological studies after the first Gulf War [76]. A subsequent analysis by the Institute of Medicine [76] concluded that having served in the military at anytime was associated with an increased risk of ALS leading to the designation of ALS as a service-connected condition in 2009 [77].

A Role for Inflammation?

Inflammatory responses occur in the brain after TBI [78•]. While acute inflammation has long been considered a transient phenomenon, there is accumulating evidence that the inflammatory response after TBI may persist. Studies in animals document persistent inflammation in brain after TBI [78•]. Markers of both a central and a peripheral inflammatory response are found in animal models after blast injury [32]. Postmortem human studies find that inflammatory changes can persist for years after TBI [79] and a recent study using positron emission tomography to image a ligand that targets microglia found increased microglial activation up to 17 years after injury [80].

Persistent inflammation has been speculated to play a role in a larger cascade ultimately leading to TBI-related dementias [78•]. Inflammation could also play a role in the frequent neuropsychiatric features associated with TBI as chronic low-grade inflammation is a consistent feature of many neuropsychiatric disorders including major depression and PTSD [81, 82]. Interestingly separate studies have found a nearly twofold increased risk of dementia in veterans with PTSD [83, 84]. Support for inflammation as a causative factor in the chronic effects of brain injury come from studies in animals showing that behavioral effects of TBI can be reversed by immunomodulatory therapy [78•].

Conclusions

Interest in military TBI has increased recently due to its frequency in the conflicts in Iraq and Afghanistan. Yet, TBI has been of long standing interest in military medicine and without doubt is a major factor in the cognitive health of veterans. Much military TBI occurs through mechanisms similar to those encountered in civilian life. By contrast certain forms of TBI are relatively unique to the military, the most prominent being blast-related TBI, which has been the major cause of TBI in the most recent veterans from Iraq and Afghanistan. Abundant evidence supports low-level blast including mTBI as having long-term effects on the nervous system with suggestions that blast-related TBI may be pathophysiologically distinct from non-blast TBI. Yet controversy continues to exist concerning the importance of blast-related mTBI in the long-term health of veterans due to the difficulty of distinguishing it from PTSD. Future research will be important for understanding in particular the mTBI/PTSD overlap.

Moderate to severe TBI may be followed by chronic cognitive impairment. TBI is also a recognized risk factor for the later development of neurodegenerative diseases in which cognitive impairment is prominent. The two diseases that have received the most attention are AD and CTE. Future research directed at understanding the relationship between TBI and subsequent dementia is a high priority, in particular understanding the factors that initiate or sustain the degenerative process. Toward this end the VA and DoD have partnered with the Alzheimer's Disease Neuroimaging Initiative (ADNI) to study the use of advanced imaging and biomarkers in determining the role that combat-associated TBI and PTSD play in increasing the risk of dementia in veterans [85]. Such studies along among other initiatives will hopefully lead to a better understanding of the military specific factors associated with cognitive impairment and how they can be treated.

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Compliance with Ethics Guidelines

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