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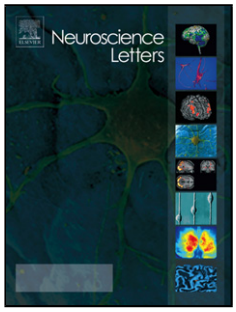

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Relationship of traumatic brain injury to chronic mental health problems and dementia in military veterans

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Highlights

- TBI caused by blast exposure is relatively unique to the military.
- Separating mild TBI from post-traumatic stress disorder is difficult.
- TBI is a risk factor for the development of neurodegenerative diseases.
- *TREM2* and *TYROBP/DAP12* link inflammation and microglia to AD and possibly TBI.

Abstract

Traumatic brain injury (TBI) is an unfortunately common event in military life. The conflicts in Iraq and Afghanistan have increased public of awareness of TBI in the military. Certain injury mechanisms are relatively unique to the military, the most prominent being blast exposure. Blast-related mild TBI (mTBI) has been of particular concern in most recent veterans although controversy remains concerning separation of the postconcussion syndrome associated with mTBI from post-traumatic stress disorder. TBI is also a risk factor for the development of neurodegenerative diseases including chronic traumatic encephalopathy (CTE) and Alzheimer's disease (AD). AD, TBI, and CTE are all associated with chronic Inflammation. Genome wide association studies (GWAS) have identified multiple genetic loci associated with AD that implicate inflammation and - in particular microglia - as key modulators of the AD- and TBI-related degenerative processes. At the molecular level, recent studies have identified *TREM2* and *TYROBP/DAP12* as components of a key molecular hub linking inflammation and microglia to the pathophysiology of AD and possibly TBI. Evidence concerning the relationship of TBI to chronic mental health problems and dementia is reviewed in the context of its relevance to military veterans.

Keywords: Alzheimer's disease; blast; chronic traumatic encephalopathy; dementia; inflammation; microglia; post-traumatic stress disorder; traumatic brain injury; TYROBP/DAP12; TREM2.

1. Traumatic brain injury in military veterans

Traumatic brain injury (TBI) is unfortunately common in both civilian and military life. TBI incidence worldwide likely approaches 10 million cases per year [54] although -- because many mild TBI (mTBI) cases go unreported -- true global incidence is probably higher and may approach 42 million per year [42]. Certain populations (such as athletes engaged in contact sports and military personnel exposed to improvised explosive device (IED) blasts on the battlefield are especially prone to TBI, leading to the identification of TBI as a major cause of combat-related disability [46].

Between 2000 and 2018, over 383,00 US service members sustained TBIs worldwide [12]. Public awareness of military-related TBI increased recently because of the frequency of TBI in the conflicts in Iraq and Afghanistan [13]. Estimates are that--of the over 1.5 million Iraq and Afghanistan veterans who had left active duty as of June 30 2012--10-20% suffered a TBI during deployment [23, 27, 51, 106]. Initially, most attention focused on the moderate to severe range of the injury spectrum, the type of TBI that would be recognized in theatre and the war in Iraq has been responsible for the greatest number of service-related severe TBIs since the Vietnam era [4]. However, what was not initially appreciated was that mTBIs were occurring but not being

recognized at the time of injury [27, 51]. Indeed, from January 2003 to October 2006, over 80% of TBIs (most of them mTBIs) suffered by U.S. troops deployed in Iraq or Afghanistan likely went undocumented [14].

2. Distinctive aspects of military TBI: the role of blast injury

As in civilian settings, military-related TBIs occur through various mechanisms including motor vehicle accidents and injuries sustained during training as well as sports or other recreational activities. Indeed, according to Department of Defense (DoD) statistics, 80% of TBIs suffered by active duty personnel occur in non-deployed settings suggesting that most military-related TBIs occur through mechanisms similar to those encountered in civilian life [23]. However, certain types of TBI are relatively unique to the military, the most prominent being TBI related to blast injury. Blast injury is an uncommon cause of TBI in civilian life [6] while blast-related mechanisms including exposures to mortars, artillery shells and improvised explosive devices (IEDs) constituted the major cause of TBI in Iraq and Afghanistan [27, 51, 106].

Primary blast injury results from transmission of an overpressure wave through tissue. Damage to tissues including the brain is thought to occur through interactions between the traveling pressure wave and the tissue itself [68]. By contrast, in blunt impact injury more typical of civilian injuries including sports and motor vehicle accidents, inertial and rotational forces combine with the direct local effects to cause tissue damage [5, 118]. In humans, high-pressure blast waves can cause extensive multi-organ trauma including severe systemic and CNS injury [30, 104, 116]. Blast injuries of this severity are without doubt a mix of injury mechanisms that include the same inertial and rotational forces associated with non-blast TBI along with the effects of the primary blast wave [30].

By contrast, although blast-related mTBI in humans probably always contains some element of rotational/acceleration injury, effects of the primary blast wave likely dominate at the lower pressure exposures associated with the mTBIs that have been so common in Iraq and Afghanistan [30]. Because of its distinctive character, injuries caused by the primary blast wave may differ mechanistically from those caused by non-blast forces remains unclear. The cerebral vasculature seems particularly susceptible to the effects of blast including low-level blast exposure with much evidence supporting a mechanism whereby the blast wave striking the body causes indirect CNS damage through pressure waves transmitted from the body [29, 36, 37]. There are also concerns over the potential adverse consequences of subclinical blast exposures. This form of blast exposure, now being referred to as military occupational blast exposure [32], is common for many service members in combat as well as non-combat settings including military breachers who use controlled explosions to gain entry to secured structures [9]. Whether repetitive low-level blast exposures may cause later health problems is unknown but is a subject of concern in the DoD and VA [32].

3. The role of TBI in the chronic mental health problems of veterans

TBI is a frequent co-morbidity in veterans seeking treatment at VA mental health clinics [7]. TBI has been linked to a variety of mental health problems including anxiety, depression, impulsivity and suicidality [24, 62]. Indeed TBI, has broad societal effects on human health, productivity and even criminality [115].

A striking feature in the most recent veterans from Iraq and Afghanistan returning with symptoms thought to be attributable to mTBI has been the frequent co-existence of post-traumatic stress disorder (PTSD) [30]. Indeed over one-third of Iraq veterans suspected of having an mTBI related postconcussion syndrome also have PTSD or depression [30, 51]. Separating what is attributable to purely psychogenic PTSD vs. what may be attributable to mTBI is often difficult due to the overlapping symptoms [30].

The controversy of psychogenic vs. physical injury is not new and dates back to debates over the causes of “shell shock”, a syndrome described during World War I, when it was first recognized that symptoms reminiscent of what might now be diagnosed as PTSD could follow blast exposures and, in particular, repetitive blast exposures [61]. While not resolved at the time [61], this controversy lives on in suggestions from the current mental health literature that postconcussion symptoms following blast-related mTBI may be better explained by PTSD or related to blast only when the TBI involved loss of consciousness which using current definition of mTBI is present in only a minority of the mTBI cases among Iraq and Afghanistan veterans [31, 50]. A 2014 Institute of Medicine report on the long-term consequences of blast injury largely echoed this notion concluding that based on human studies there was “limited/suggestive evidence that most of the shared symptoms are accounted for by PTSD and not a direct result of TBI alone.”

PTSD and mTBI might coexist due to additive effects of independent psychological and physical traumas experienced in a war zone. Alternatively, blast injury might induce PTSD-related traits or damage brain structures that mediate responses to psychological stressors, increasing the likelihood that PTSD will develop following a subsequent psychological stressor. The two disorders have an interesting relationship in that they can be viewed as different ends of a spectrum with TBI being the prototypical organic brain disease requiring a blow to the head. By contrast, PTSD is conceptualized as being rooted in a psychologically based reaction to a stressor that was unassociated with physical injury. Separating the two disorders clinically remains challenging because of the overlapping symptoms [31].

The distinction between blast-related brain injury and PTSD has more than academic significance because it affects treatment strategies as well as patient education. Current treatment of PTSD emphasizes psychological interventions with cognitive behavioral therapies including prolonged exposure therapy as well as pharmacologically-based treatments with agents such as selective serotonin reuptake inhibitors [100]. By

contrast, TBI treatments are based on an organic model that presumes structural brain alterations have occurred and that recovery depends on restoration of neurological factors. Treatments focus on improving attention and concentration with agents such as psychostimulants, or improving compensatory strategies through cognitive behavioral therapies. However, pharmacological interventions that improve one condition may worsen the other [78]. For example, α-adrenergic blockers such as prazocin, which are given to improve sleep in PTSD, may worsen TBI-related cognitive complaints, and agents that improve cognitive function, such as psychostimulants, may exacerbate PTSD symptoms. It is also possible that persistent cognitive deficits associated with TBI may complicate cognitive-behavioral approaches to PTSD because both exposure- based and cognitive-behavioral interventions depend on some measure of cognitive reserve, making it plausible that cognitive deficits associated with TBI may reduce responsiveness to PTSD therapies.

Rats exposed to repetitive low-level blast exposures that induce little overt CNS pathology nevertheless induce PTSD-related behavioral traits [28, 91]. Because these blast exposures occur under general anesthesia, it appears that blast exposure in the absence of a psychological stressor induces chronic PTSD-related traits. These traits have been observed to be present for at least 9 months after the last blast exposure [91]. Furthermore, if blast-exposed animals are challenged with a predator scent 8 months after the last blast exposure, even a single exposure induces new anxiety-related changes that are still present 45 days after the challenge [92]. Such a reaction to a predator scent delivered many months after blast exposure suggests that blast exposure sensitizes the brain to react abnormally to subsequent psychological stressors. Supporting an effect of TBI in humans, neuroimaging studies have found chronic decreases in fractional anisotropy in dual diagnosis veterans that are suggestive of axonal injury and unlikely to be explained by co-morbid PTSD [31].

Thus, while one body of research suggests that much of what is presently being called postconcussion syndrome secondary to blast-related mTBI is clinically identical to what has classically been described as PTSD, other evidence suggests that low-level blast exposure may induce PTSD-related traits without the need for a psychological stressor. Development of PTSD-like behavioral related traits in the absence of a psychological stressor suggests the existence of what we call blast-induced PTSD or blast-related PTSD [93].

4. The role of TBI in dementia in veterans

TBI may be associated with persistent cognitive deficits with as many as two-thirds of moderate to severe TBI victims being left with long-term cognitive deficits and nearly 25% of these victims failing to return to work in the year following injury [98]. A study of predominately Iraq or Afghanistan veterans who suffered moderate to severe TBIs found that about half remained symptomatic in some form three years after injury [8]. More recently, it has become recognized that TBI is a risk factor for the later

development of dementia [22, 111]. One study [2] revealed that, in older veterans, any history of TBI conferred a 60% increase in the risk of developing dementia over a 9-year period. 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 without a TBI history [3, 19]. A prospective study of older World War II veterans revealed that those with remote histories of moderate-to-severe TBIs had a two- to fourfold increased hazard ratio for developing dementia in [96]. Because of its frequent occurrence during military service, the relationship of TBI to later life cognitive impairment in veterans is an issue of much concern.

Whether mTBI increases risk for later life cognitive impairment is less conclusive. Prior systematic reviews and a 2008 Institute of Medicine report suggested no increased risk for later life dementia after an mTBI if there was no loss of consciousness [3, 19]. A study of World War II veterans also revealed no increased risk for dementia with a history of mTBI [96] although another study recently suggested that mTBI may be a risk factor for developing dementia if it occurs after age 65 [41]. Data from a recent meta-analysis led to the conclusion that a history of TBI (including mild TBI) was associated with an increased risk for the development of AD, Parkinson's disease and a variety of mental health disorders [94]. Another study of Iraq and Afghanistan veterans suggested that mTBI might act in combination with genetic risk factors for AD [49]. Thus, the relationship of mTBI to later cognitive impairment remains disputed and may be complex. Where there is no dispute is the relationship of repetitive mTBI with the entity now known as chronic traumatic encephalopathy (CTE) [40], which is discussed below.

Dementia following TBI is best recognized as the sequelae of the type of blunt force trauma common in both civilian and military settings. Whether blast exposure with its apparently distinctive physical character and likely pathophysiological basis is also a risk factor for later dementing illnesses is unknown. In particular, little is known about long-term outcomes following blast related mTBI, although one study of 167 U.S. military service personnel evaluated within 5 years of sustaining an mTBI during operations in Iraq and Afghanistan revealed that while many subjects improved, ≈ 20% reported new symptoms [69]. How these symptoms will change over time is unknown.

5. Chronic traumatic encephalopathy

In 1928, Martland reported an association between repetitive mTBI and chronic progressive neurologic dysfunction in boxers [77]. Similar cases of this condition, which Martland referred to as “punch drunk” in the title of his original paper were described by others and the syndrome came to be known as *dementia pugilistica* [40]. The neuropathology of this syndrome (the name of which later reverted to the original term of CTE) was described in autopsy studies in the 1960s and 1970s [18]. Recent interest in this disorder was stimulated when, in 2005, Omalu described CTE in an American professional football player [90]. The condition has now been particularly recognized in former American football players with Mez *et al.* [84] recently finding 177 cases of

pathologically confirmed CTE in a sample of 202 former players, including high school, college and professional level athletes with the disease being present at postmortem in 110 of 111 former NFL players who presented with clinical CTE during life. CTE has also been reported in other sports including hockey, soccer, rugby and professional wrestling [40, 76, 79-81, 83, 84] as well as in military veterans [44, 82, 89].

Clinically, CTE typically presents following a latent period of years to decades after the repetitive trauma [40]. Subtle behavioral changes including alterations in mood or personality along with apathy, poor impulse control or aggression are frequent presenting features. Cognitive impairment is usually less apparent initially than the behavioral features. Symptoms begin insidiously but once initiated the course is typically one of 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 was present in only a minority [81]. CTE may be associated with Parkinsonian features (previously known as *pugilistic parkinsonism*) or motor neuron disease [40, 79, 81]. Extrapyramidal and motor neuron-related features, when present, usually appear later in the disease. As in AD, apolipoprotein E genotype appears to influence susceptibility to CTE and other genetic risk factors are also likely [40].

At the neuropathological level, CTE is primarily a tauopathy with aggregates of phosphorylated tau deposited as neurofibrillary tangles (NFT) in neurons and astrocytes [40, 79, 81]. Histologically, NFTs in CTE resemble those found in AD but differ in distribution [79, 81] as well as fine structure [34] and aggregation properties [67]. Unlike the pattern of NFTs in AD which first appear in transentorhinal areas before spreading to limbic structures and then neocortical regions [103], in CTE, neuronal and astrocytic aggregates are concentrated in the superficial cortical layers and the depths of the sulci [79, 81]. Prominent neuronal NFTs are also found in perivascular locations [79, 81]. While diffuse amyloid plaques are frequently present in CTE, the neuritic plaques characteristic of AD are typically absent [79, 81].

A concern for CTE might be raised particularly in the most recent veterans because of the frequency repetitive mTBI in Iraq and Afghanistan [30, 51], and indeed, there have been now at least five cases of CTE reported in Iraq and Afghanistan veterans. Omula *et al*. [89] reported the first in a 27-year-old Marine who was deployed twice to Iraq where he was exposed to repetitive blasts although no clinical TBIs were documented. He suffered an mTBI while playing football and was in a motor vehicle accident between deployments. Following a second deployment to Iraq, he developed a progressive cognitive and behavioral syndrome that was diagnosed as PTSD. At autopsy, his brain showed NFTs in a multifocal pattern characteristic of CTE. Goldstein *et al.* [44] reported four more cases in Iraq and Afghanistan veterans who were exposed to blast or concussive injury. Neuropsychiatric features (including depression, anxiety, and cognitive decline) were described in three of the four. Two of these three had a PTSD-like syndrome. A fourth case was described as having headaches, irritability and

depression as well as poor sleep and concentration. The only history of TBI in this last patient who died from a ruptured basilar artery aneurysm was exposure to a single close-range IED explosion that caused a 30 min period of disorientation without loss of consciousness. At autopsy, all patients had perivascular and deep sulcal accumulations of tauopathy in neurons and glial cells as well as dystrophic axons, features consistent with CTE. In McKee's large autopsy series of CTE [83], which included the four cases reported by Goldstein [44], there were 21 military veterans among 85 cases. Sixteen of the 21 veterans were also athletes including eight NFL players. Only three veterans in this series had been exposed to blast.

How much of the vulnerability of veterans to CTE is attributable to their military exposures is unknown. Attempts to estimate prevalence are limited by the lack of consensus criteria for the clinical diagnosis of CTE, which at present is a neuropathological diagnosis [79]. Indeed, the true prevalence of CTE in populations clearly at risk such as NFL football players is uncertain due to ascertainment bias in all series. CTE may also be present along with other disorders. In the 68 cases of McKee *et al.* [83], published in 2013, CTE was the sole diagnosis in only 63% with other diagnoses including AD, Lewy body disease and frontotemporal lobar degeneration present in many of those remaining, suggesting that other neurodegenerative disorders frequently co-occur. Whether blast exposure represents a unique risk factor for military veterans -- especially those returning from the most recent conflicts -- is unclear. Animal studies show that blast induces multiple aberrantly phosphorylated tau species acutely, some of which are still present up to 30 days later [44, 53]. Yet few cases of CTE have been reported in veterans although studies revealed higher levels of exosomal tau in the peripheral blood of military personnel who had suffered mTBIs and were experiencing chronic symptoms [43]. A recent study of non-demented Vietnam era veterans using the tau Positron Emission Tomography (PET) ligand [(18)F] AV145 also found that those with a history of TBI, PTSD or both disorders exhibited increased ligand binding compared to controls [85]. Whether these military veterans are at increased risk of CTE is unknown.

6. Alzheimer's disease

As the most common cause of senile dementia in the Western world, AD will affect a growing population of aging veterans posing heath care challenges for the Department of Veterans Affairs [105]. For reasons that are not fully understood, military veterans appear to be at increased risk of AD. In 2013, Veitch *et al.* [110] estimated that -- among 423,000 new cases of AD then expected to appear in veterans by 2020 -- an excess of 140,000 cases would be attributable to military exposures. The reason for this excess among military veterans is probably multifactorial with TBI likely being one such factor [110, 111].

A link between single moderate or severe TBI and the later development of AD has been supported by multiple studies [3, 22, 35, 96]. A meta-analysis of 15 case-control studies found that in males a single TBI that was associated with loss of consciousness

lead to a 50% increased risk of AD [35]. Other studies link TBI with an earlier age of onset [87]. Similar trends are observed in military veterans. One study in World War II veterans revealed that those with a history of severe TBI were 4 times more likely to have AD [96]. Risk increased two-fold in veterans with moderate TBI while a history of mTBI appeared to confer no increased risk [96].

The conventional wisdom regarding why TBI might be associated with an increased risk for AD has largely centered on the acute effects of TBI on processing of the β-amyloid (Aβ) peptide. Aβ is deposited in the amyloid plaques found in AD with the longer Aβ42 species thought to be the most neurotoxic and associated with a sequence of pathological events [39]. Aβ accumulates rapidly following TBI [21, 22, 55, 109]. In humans, diffuse cortical plaques and increased levels of soluble Aβ are found within hours of a severe TBI [21, 22, 55]. Aβ is also elevated in animal models of cortical impact TBI 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 towards the Aβ pathway [74]. As in AD, genetic risk factors such as apolipoprotein E likely influence TBI-related effects [70]. Recently in military personnel Aβ 42 has been found to be chronically elevated in peripheral blood in mTBI cases experiencing chronic postconcussive symptoms [43]. Thus, TBI may initiate a pathological shift in Aβ production, which may -- as in AD unassociated with TBI -- begin decades before the onset of symptoms.

Whether blast injury with its distinctive character puts veterans returning from the recent conflicts in Iraq and Afghanistan at especially increased risk of AD is unknown. However, curiously, when Aβ levels were examined in rats and mice following blast exposure, rather than increasing, Aβ levels in brain decreased acutely [20]. Also, unlike cortical impact models in animals, BACE-1 and the γ-secretase component presenilin-1 were unchanged following blast exposure in rats [20]. Axonal accumulation of APP, a hallmark of acute axonal injury in non-blast TBI [95] also appears to be an inconsistent feature of blast-related TBI in animals [20]. The unexpected lowering of Aβ by blast again raises the question of whether blast-related TBI is pathophysiologically distinct from non-blast TBI.

7. TREM2 and TYROBP/DAP12 as a key molecular hub linking inflammation and microglia to the pathophysiology of AD

Most cases of AD occur sporadically without known environmental or genetic causes. However, in a subset of cases the disease is inherited in an autosomal dominant manner [102]. Such cases of familial Alzheimer's disease (FAD) typically have an earlier age of onset than the more common sporadic cases. Mutations causing FAD have been found in the genes for the *amyloid precursor protein*, *presenilin 1*, and *presenilin 2* [102]. While rare because these mutations all affect production of the longer, more amyloidogenic forms of the Aβ peptide, they provided strong support for the amyloid

hypothesis of AD [39]. By contrast polymorphisms in the *apolipoprotein E (APOE)* gene confer strong genetic risk for sporadic cases of AD [17]. Apolipoprotein E likely exerts its effects through both Aβ dependent and Aβ independent mechanisms [73]. Genome wide association studies (GWAS) have confirmed that the *e4* allele of *APOE* is the strongest genetic risk factor for AD, conferring increased risk in both early onset and late onset cases [73].

GWAS studies have in addition identified more than 20 genetic loci that while conferring far lower individual genetic risk than *APOE* have become of interest because they implicate inflammation and in particular microglia as key modulators of the AD degenerative process [47, 88]. Microglia are the innate immune cells of the CNS originating from cells in the embryonic yolk sac that migrate into brain during embryonic life [26, 71]. Reactive microglia are found around amyloid plaques in AD where their functions are likely complex but are thought to play -- at least in part -- protective roles removing compacted amyloid fibrils or possibly converting them into a less toxic form [47, 88, 117].

Of particular importance has been discovery of AD-associated polymorphisms in the *TREM2* (triggering receptor expressed in myeloid cells 2) gene [16]. TREM2 is a cell surface receptor that is selectively expressed on microglia and certain myeloid cells in the periphery. TREM2 interacts with the activating adaptor protein DAP12 (encoded by the TYRO protein tyrosine kinase-binding protein gene, *TYROBP,* also known as *DAP12*). TREM2 stimulation initiates signal transduction pathways that promote microglial proliferation, survival, chemotaxis and phagocytosis [16, 108, 124]. Extracellular ligands of TREM2 include ApoE and Aβ [120, 123].

The R47H variant in *TREM2* is the mutation most strongly associated with AD increasing risk by about threefold, although other mutations in TREM2 are also more common in AD [75]. The R47H as well as other mutations in TREM2 appear to be loss-of-function mutations that impair microglial activation and phagocytosis arguing that normal microglia protect against AD [47, 66]. Consistent with this notion, mice with null mutations in TREM2 have reduced microglial reactivity and show impaired microglial migration [57]. Mice expressing the TREM2 R47H mutation also display abnormal macrophage behavior and fail to mount pro-inflammatory responses including production of pro-inflammatory cytokines to challenges of the innate immune system with agents such lipopolysaccharides [15]. Furthermore, uptake of Aβ by TREM2-deficient microglia is impaired [120], suggesting that TREM2 impaired Aβ clearance might, at least in part, explain how TREM2 mutations increase the risk of developing AD.

The impact of TREM2 on AD-related pathology has been investigated in several AD-related mouse models of amyloidosis. These studies have been consistent in showing that absence of TREM2 attenuates inflammation-related gene expression [57, 112] while reducing microglial infiltration around amyloid plaques [57, 108, 113]. The impact on amyloid pathology has been more complex. Consistent with TREM2 having a

neuroprotective role in AD, when wild type TREM2 was overexpressed in brain by intracerebral lentiviral injection into 7-month-old APP/PS1 mice, Aβ plaque load decreased and Morris water maze performance improved [58]. Studies in which amyloid-depositing mouse models were bred onto the TREM2-/- background have revealed either reduced or no change in amyloid pathology at young ages [57, 113] while Aβ plaque loads were increased in older mice [56]. TREM2 deficiency or haploinsufficiency also impaired microglial responses and worsened amyloid plaque load in 5xFAD mice [112].

Altering TREM2 expression in tau transgenic mice has produced conflicting results. When the PS19 human tau transgenic line was bred onto the TREM2-/- background neuroinflammation including microglial activation was attenuated and the mice were protected against neurodegeneration [72]. By contrast, when TREM2 expression was knocked down by lentiviral injection in P301S tau transgenic mice, tau pathology, neurodegeneration and spatial learning deficits were exacerbated [59].

Strengthening the importance of the TREM2 pathway, an independent computational approach revealed that an AD-related network was centered around the TREM2 binding partner TYROBP/DAP12, as identified by Zhang *et al.* [122]. TYROBP/DAP12 was identified as a key network hub when gene regulatory networks were examined in postmortem brain tissues obtained from controls and subjects with late-onset Alzheimer's disease (LOAD). Through an integrative network-based approach, they identified a microglial-specific module that contained as a key regulator TYROBP/DAP12, which was upregulated in LOAD. Overexpression of TYROBP/DAP12 in mouse microglia produced expression changes that greatly overlapped many of the changes in the human brain TYROBP/DAP12 network [122].

Since overexpression of TYROBP/DAP12 seemed to mimic or exacerbate AD pathology, Haure-Mirande *et al*. [48] determined whether reduction of TYROBP/DAP12 might mitigate AD-related changes in a mouse model of Aβ amyloidosis. They observed that absence of TYROBP/DAP12 in mice expressing the *APP* $^{KM670/671NL}$ */ PSEN1* $^{\Delta exon9}$ familial AD mutations reproduced the expected network characteristics by normalizing the transcriptome of APP/PSEN1 mice as well repressing induction of genes involved in the switch from homeostatic microglia to disease-associated microglia, including TREM2, complement (C1qa, C1qb, C1qc, and Itgax), Clec7a and Cst7. Furthermore, absence of TYROBP/DAP12 protected the mouse from the effects of amyloid toxicity since the typical electrophysiological and learning deficits were eliminated while having no effect on the burden of amyloid and Aβ [48] .

In a related study, Audrain *et al.* [1] crossed mice expressing the human *MAPT* ^{P301S} mutation associated with human frontotemporal dementia and Parkinsonism (FTLD-17) onto the TYROBP/DAP12 null background. Paradoxically, biomarkers associated with a worsened behavioral phenotype (including increased hyperphosphorylated tau) increased when the MAPT transgene was expressed on a TYROBP/DAP12 null

background, despite the observation that mice deficient in TYROBP/DAP12 exhibited better synaptic function and learning relative to MAPT transgenic mice with normal levels of TYROBP/DAP12. Consistent with predictions that complement reduction exerts a neuroprotective effect, levels of the complement cascade initiator C1q were reduced in *MAPT^{P301S} X Tyrobp/Dap12(-/-)* mice [1].

8. Role for microglia and chronic inflammation in TBI

Inflammatory responses have long been known after closed impact injuries in humans and in animal models of TBI [33]. While often thought of as a transient phenomenon, there is accumulating evidence that the inflammatory response may evolve into a chronic one [33, 65]. In humans, postmortem studies have revealed that inflammatory changes can persist for years after TBI [60]. Speculations are that persistent inflammation plays some role in initiating a larger cascade that ultimately leads to TBI-related dementias [33, 65]. It is also tempting to speculate that inflammation could play a role in the neuropsychiatric features associated with TBI since chronic low-grade inflammation is a feature of many neuropsychiatric disorders including PTSD and major depression [86, 114]. Supporting a role for inflammation as a causative factor are studies showing that some behavioral effects of TBI in animal models can be reversed by immunomodulatory therapy [33, 65].

As in AD, microglia have been implicated as key mediators of the chronic inflammation that follows TBI in animal models [64, 121]. In humans, positron emission tomography (PET) imaging using a ligand that targets microglia has revealed increased microglial activation up to 17 years after injury [99]. TREM2 has also been implicated as playing a role in the molecular pathophysiology of injury and recovery after TBI [10, 11, 97, 101]. Following lateral fluid percussion injury, TREM2 expression increased in wild type C57BL/6 mice and *Trem2 -/-* mice exhibit better recovery [101]. In a study designed to determine the effects of *APOE* genotype on TBI responses, Castranio *et al.* [10] performed controlled cortical impact injuries on 3-month-old mice expressing human *APOE3* or *APOE4* isoforms. Following injury, they found that both *APOE3* or *APOE4* replacement mice exhibited cognitive deficits compared to mice with wildtype mouse *APOE*. Transcriptional profiling and gene network analysis on RNA collected 14 days after injury revealed that the network mostly correlated to TBI in animals expressing both human *APOE* isoforms was an immune response network with major hub genes that included TREM2 and TYROBP/DAP12. Increased TREM2, IBA-1 and glial fibrillary acidic protein (GFAP) protein was observed in the brains of TBI-injured mice [10]. In a related study, ABCA1 haplodeficiency on a humanized *APOE4* background also affected the transcriptional response to TBI with hub genes that included TREM2 and TYROBP/DAP12 [11].

Central and peripheral inflammatory responses are observed in animal models following exposure to blast injury [25, 29, 45, 52, 63, 107, 119]. These studies, which were mostly performed using higher-level blast intensities, clearly document a

prominent microglial response during the acute to subacute time window following blast injury. To date, less is known about the chronic neuroinflammatory response following blast injury and the one study to date that examined inflammation in a model of repetitive low-level blast found no evidence of microglial changes or changes in brain or plasma inflammatory cytokines at 40 weeks after injury despite the presence of a chronic behavioral phenotype at this age [38, 91]. Thus, the role of chronic neuroinflammation following blast remains unknown.

9. Conclusions

TBI is a subject of long-standing interest in military medicine. TBI has gained greater public awareness recently due to the conflicts in Iraq and Afghanistan. Blast-related TBI is a form of injury relatively unique to the military. The differentiation of blast-related TBI from PTSD has been an issue of concern in the most recent veterans. TBI confers risk for the later development of neurodegenerative diseases, the best-established relationship being the connection between repetitive mild TBI and CTE. However, moderate to severe TBI and possibly even mTBI may be risk factors for the later development of AD. Chronic inflammation is thought to play a role in AD, TBI and CTE. GWAS studies have identified genetic loci associated with AD that implicate inflammation and microglia as involved in the degenerative process. In particular, TREM2 and TYROBP/DAP12 have been identified as part of a molecular pathway that seems to link microglia to the pathophysiology of AD and possibly TBI as well.

Competing interests

The authors declare that they have no competing interests.

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