

RESEARCH REVIEW ON TRAUMATIC BRAIN INJURY, IRRITABILITY, AND AGGRESSION

OVERVIEW

The purpose of this research review is to summarize recent developments in the scientific literature on relationships between traumatic brain injury (TBI), irritability, and aggressive behavior. TBI is a significant health issue in military and veteran populations. (Defense and Veterans Brain Injury Center (DVBIC) & Defense Centers of Excellence for Psychological Health and Traumatic Brain Injury (DCoE), 2014; Institute of Medicine of the National Academies, 2009). Irritability and aggressive behavior can stress family, social, and professional relationships. Aggressive behavior can interfere with employment and rehabilitation and may lead to legal consequences. We describe research findings on prevalence and risk factors for irritability and aggressive behavior in individuals with TBI history. We also discuss risk factors for aggressive behavior in non-clinical military/veteran and civilian populations, and findings regarding TBI and legal involvement potentially due to aggressive behavior. To give the reader a global perspective on aggression, studies included cover all severities of brain injury from mild to severe and penetrating.

BLUF

TBI is often associated with neurobehavioral changes including increased irritable feelings, and may be associated with aggressive behavior. (Baguley et al., 2006; Kim et al., 1999) These changes may be more pronounced in those with moderate and severe TBI history, and may be accompanied by a lack self-awareness of these and other symptoms. (Yang et al., 2013) The most common form of aggressive behavior in this population is verbal aggression. (Sabaz et al., 2014)

Predictors of aggressive behavior (as defined in this research review) after TBI in civilian populations include current or pre-injury substance abuse or mood disorder, and history of aggression. (Tateno et al., 2003) Population studies of veterans and returning service members indicate that PTSD symptoms, mood disorder or suicidality, substance misuse, lower education, and history of arrest or domestic violence are associated with aggressive behavior and legal consequences thereof, while TBI status is generally not as strongly associated with aggressive behavior as other factors. (Elbogen et al., 2012; Gallaway et al., 2012; Macmanus et al., 2012; Rosellini et al., 2015) Pharmacological (Plantier et al., 2016) and non-pharmacological (Luaute et al., 2015; Wiart et al., 2016) interventions for irritability and aggressive behavior after TBI show promise, but evidence is limited. Existing clinical practice guidelines recommend evaluation and treatment of any psychiatric comorbidities occurring in persons with a history of mTBI.

BACKGROUND

TBI Definition

Traumatic brain injury is a physiological disruption or structural injury to the brain resulting from external forces that manifests as a broad spectrum of symptoms and disabilities.

The etiology of TBI may vary: blunt head trauma, acceleration or deceleration forces, or exposure to blast. The Department of Defense (DoD) definition of TBI categorizes closed-head injuries as mild, moderate, or severe based on characteristics described in Table 1. (Department of Defense & Department of Veterans Affairs, 2009) Mild TBI, or concussion, is much more common than moderate or severe TBI. (Defense and Veterans Brain Injury Center (DVBIC), February 2015) Symptoms for mild TBI (mTBI) typically include headache, fatigue, dizziness, or memory deficits, and most individuals experience resolution of symptoms within one to three months. (Department of Defense & Department of Veterans Affairs, 2009)

Moderate and severe TBI are associated with more severe symptoms, and have a longer recovery period. Outcomes for severe TBI often involve some level of longer-term disability. Emotional and behavioral symptoms following TBI of any severity can include feeling depressed, anxious, impatient, irritable, or having mood swings. (Deb et al., 1998, 1999; Hibbard et al., 1998; Horner et al., 2008)

Table 1. Definition of mild, moderate, and severe TBI (Department of Defense & Department of Veterans Affairs, 2009)

Criteria	Mild	Moderate	Severe
Structural imaging (i.e., computed tomography; CT)	Normal	Normal or Abnormal	Normal or Abnormal
Loss of consciousness (LOC)	0-30 min	> 30 min and < 24 hrs	> 24 hrs
Alteration of consciousness (“dazed” feeling, confusion)	≤ 24 hrs	> 24 hrs	> 24 hrs
Post-traumatic amnesia (PTA)	≤ 24 hrs	> 24 hrs and < 7 days	> seven days
Acute Glasgow Coma Scale (GCS)	Score 13-15	Score 9-12	Score 3-8

Aggression and irritability definition

Irritable mood is described in the DSM-IV as featuring “persistent anger, a tendency to respond to events with angry outbursts or blaming others, an exaggerated sense of frustration over minor matters.” (American Psychiatric Association, 1994, 2013) For purposes of assessment, irritability can be conceptualized both in terms of subjective internal experience (e.g., anger, annoyance, or impatience) and observable behavior (e.g., verbal aggression). Aggression can be an expression of anger or irritation and can occur in verbal and/or physical forms. Physical aggression can be directed against objects, persons, or self. In persons with a history of TBI, aggression may arise from a combination of neuropsychological and emotional dysfunction, such as increased frustration and decreased inhibition and tolerance. (Alderman, 2003) Both irritability and aggression can be measured by self-report scales and clinician or proxy scales. If irritability or aggression after TBI cause “clinically significant distress or impairment in social, occupational, or other important areas of functioning,” the individual can be diagnosed with a personality change due to another medical condition, aggressive type. (American Psychiatric Association, 1994, 2013)

Studies included here define aggression according to the Overt Behavior Scale, (Kelly et al., 2006) the Overt Aggression Scale (OAS), (Yudofsky et al., 1986) neurobehavioral scales, or other measures. These scales collect information on behaviors including shouting, swearing, throwing or breaking objects, self-cutting, and striking and kicking others. The Overt Behavior Scale provides scores on the severity, frequency, and impact of nine categories of behavior, six of which are aggressive. The OAS divides aggressive behavior into four categories: verbal aggression, and three categories for physical aggression directed against objects, the self, or others. In each of the four subscales, a range of behaviors are queried. For example, from the physical aggression against objects subscale, the behaviors range from slamming doors to throwing objects in dangerous fashion.

This research review includes studies with clinician-reported outcomes, family-reported outcomes, self-reported behavior, and/or self-reported psychological symptoms. Self-harm is included in some aggression outcomes reported here, but suicidality will be discussed in another research review. Most outcomes discussed are behavioral, but some studies include outcomes or indications relating to anger and impulsivity, which are internal states or personality traits rather than outwardly visible behaviors.

PREVALENCE OF IRRITABILITY AND AGGRESSIVE BEHAVIOR AFTER TBI

Prevalence of irritability after mTBI

Some small civilian studies with mTBI have found that irritability symptoms occur in more than one-third of participants, but results vary widely based on varied assessment methods. A study by Dikmen, et al. surveyed 68 individuals with mTBI and found that 36% endorsed irritability on a symptom checklist at one year post-injury. (Dikmen et al., 2010) A retrospective study by Johansson et al. included 49 participants with mTBI history (mean time since injury was 25 months, standard deviation, SD, 19 months), recruited from an outpatient neuropsychology office, of whom 76% reported irritability or aggression in clinician interviews. (Johansson et al., 2008) The high prevalence in this study may have been due to the selection of care-seeking individuals. Yang, et al. administered questionnaires to 50 participants with mild TBI history. The overall post-injury irritability scores were higher than those of uninjured controls, but did not differ significantly from pre-injury scores except for the annoyance subscale. (Yang et al., 2013) The retrospective scale used for pre-injury scores may have had limited accuracy. Studies using symptom checklists such as the Neurobehavioral Symptom Inventory (NSI) and Rivermead Postconcussive Symptom Questionnaire (RPQ) have found that a significant fraction of civilians without mTBI history endorse irritability, although average irritability scores are higher among those with mTBI history. (King et al., 2012; Zakzanis & Yeung, 2011)

A study by Bailie et al. examined data regarding feelings of anger among 363 active duty service members with mTBI within 36 months, grouped based on the remoteness of injury. Results showed that the frequency of abnormally high anger scores was 54% among those with mTBI within the last 0 to 3 months. (Bailie et al., 2013) The frequency of high anger scores was lower in groups with more remote injury, and the lowest frequency was 39%, among those with 13 to 36 months since injury. Hoge et al. collected surveys from 2525 recently returned OEF/OIF veterans, and found that 48% to 57% of those with mTBI history reported irritability. However,

when the results were adjusted for PTSD and depression, there was no significant difference in irritability between the TBI group and the group with non-TBI injuries. (Hoge et al., 2008)

Prevalence of irritability in mixed severity TBI groups

Overall, estimates of irritability prevalence among individuals with TBI of any severity range from 15% to 75%. Several early studies assessing groups of individuals with mixed severity TBI history showed that 30-34% of participants report or meet criteria for irritability at 3, 6, 9, or 12 months post-injury. (Deb et al., 1998; Kim et al., 1999; van der Naalt et al., 1999)

In a study of irritability by Yang et al. with 64 individuals with TBI (mean GCS score 12.2; SD, 3.7), post-injury irritability was identified in 15% of the participants according to a self-report scale, and in 29% according to family member reports. Subscores for verbal aggression and annoyance were also higher post-injury on both the self and family member reports. (Yang et al., 2012) Johansson et al. reported irritability or aggression in 75% of 67 individuals with TBI history assessed by clinician interview at an outpatient neuropsychology office. Family members also reported a higher occurrence of verbal aggression and annoyance than the subjects self-reported, suggesting that self-report data may underestimate the presence of these outcomes, perhaps due to lack of awareness in individuals with TBI (anosognosia). (Yang et al., 2013) A 2001 investigation interviewed 563 individuals who had sustained a moderate or severe TBI 3 months to a few years prior. In semi-structured interviews with patients and family members, 19% of participants with TBI had problems with irritability and 21% had problems with anger management. Among the 139 of these individuals who returned to driving after head injury, 25% reported irritability. (Hawley, 2001)

Prevalence of aggression in mTBI and mixed severity TBI groups

A number of studies have shown that a minority (24% to 34%) of individuals with TBI of any severity demonstrate aggressive behavior including verbal aggression and aggression against objects. Tateno et al. evaluated 89 civilian patients with TBI (57% mild, 22% moderate, 22% severe) who were mostly motor vehicle accident survivors within 6 months of injury. Subjects were divided into aggressive and non-aggressive groups based on whether they self-reported four or more episodes of aggressive behavior since injury and had an OAS score of 3 or greater. Aggressive behavior was observed in 34% of the sample. (Tateno et al., 2003) In a 2009 study by Rao, et al. on 67 participants with TBI of mixed severity (60% mild TBI, mean GCS score 12.2) aggression was assessed at three months post-injury and defined as endorsing any aggression subtype screening question on the Overt Aggression Scale (OAS). (Rao et al., 2009; Yudofsky et al., 1986) Among the 41 participants with LOC of less than 30 minutes (i.e., probable mild TBI), 24% presented aggressive behaviors. Among those who did show aggression (N = 19, including 10 with mild TBI history and 9 with moderate or severe TBI), verbal aggression was the most common symptom, specifically making loud noises and shouting angrily. No participants displayed aggression against themselves or others. (Rao et al., 2009) Participants in this study had a high rate of pre-injury Axis 1 psychiatric diagnosis (76%) and alcohol (52%) or substance (49%) abuse/ dependence, and results may not be generalizable to populations with lower rates of co-morbidity.

Research on mild TBI more often focuses on irritability and anger, but a few studies have examined self-reported aggressive behavior in this population. Johansson et al. interviewed 49

individuals with mild TBI at an outpatient neuropsychology office and found that 33% reported at least aggression towards objects when evaluated an average of about 2 years after injury. Among the 18 individuals with moderate or severe TBI history included in the same study, 44% reported at least aggression towards objects. (Johansson et al., 2008) A recent study of 797 former college athletes showed that those reporting three or more concussions had higher aggression and depression scores compared to those with no concussion history. Higher impulsivity scores were also found in those reporting two or more concussions. (Kerr et al., 2014)

Prevalence of aggression after moderate and severe TBI

Studies indicate that aggressive behavior, particularly verbal aggression, is prevalent in those with moderate and severe TBI, although data vary widely. A study of 507 individuals with severe TBI recruited from an Australian outpatient rehabilitation program evaluated clinician-reported data from the Overt Behavior Scale. Researchers found verbal aggression in 27% of the sample, physical aggression against objects in 8%, physical aggression against self in 5%, and physical aggression against others in 10% of the sample. (Sabaz et al., 2014) Time since injury ranged from less than 1 year to more than 5 years. A retrospective study of 228 consecutive patients with moderate (32%) and severe (68%) TBI treated at an inpatient rehabilitation center found that 60% of patients endorsed any one of the OAS subscales 24 months after rehabilitation admission. The authors defined aggression as an OAS score of 7, which indicates a “considerable degree of aggressive behavior, occurring on at least 2 subscales and involving some degree of actual physical aggression,” and found that about 25% of the sample was aggressive at each time point (6, 24, and 60 months after rehabilitation admission). (Baguley et al., 2006) The higher level of aggression observed in the sample recruited from the inpatient rehabilitation center may have reflected a different patient population.

The study by Hawley et al. in which 563 individuals with TBI history were interviewed about symptoms found that 7% of participants had problems with aggression, and 5% had problems with frustration. Remarkably, 48% of participants had any behavioral problem including irritability, anger management issues, temper or abusive behavior, aggression, or frustration. (Hawley, 2001) The authors did not clearly define the difference between irritability, aggression and other behavioral issues.

Salazar et al. conducted a study with 120 active-duty military personnel with moderate or severe TBI that included self-reported behavior outcomes. At baseline (average 38 days post-injury), 18-19% of the sample reported aggressive behavior, and 9-10% reported violent behavior. Aggression and violence were assessed by the Present State Exam. After 1 year, prevalence of aggressive behavior had increased to 37-41% of the sample. (Salazar et al., 2000)

Aggression after penetrating frontal lobe injury

Studies on frontal lobe penetrating injury and aggression are limited due to the rarity of this type of injury, and existing literature is limited by incomplete reporting on known correlates of aggressive behavior, including substance misuse and prior history of aggressive behavior. However, evidence suggests that damage to the frontal lobe from penetrating brain injury is strongly correlated with aggressive and antisocial behavior.

Arguably the most famous TBI patient in history, 19th century railroad worker Phineas Gage, experienced a profound personality change after a severe penetrating injury to the frontal ventromedial cortex. (Dimitrov et al., 1999) Similar cases have been described of what has come to be called frontal lobe syndrome, in which a frontal lobe injury causes antisocial behavior. (Dimitrov et al., 1999; Raymond et al., 2011; Saout et al., 2011; Sugden et al., 2006) Injury to the frontal lobe is not consistently associated with aggression-related outcomes in groups with moderate or severe closed-head TBI history. (Elbogen et al., 2014; Tateno et al., 2003) Neuroimaging studies of persons exhibiting antisocial or violent behavior have shown that, independent of TBI status, prefrontal structural abnormalities and prefrontal functional impairments are associated with these behaviors. (Yang & Raine, 2009)

Systematic studies of war veterans have found an association between penetrating frontal lobe injuries and aggressive or antisocial behavior, including several studies of World War II veterans. (Brower & Price, 2001) Results from the Vietnam Head Injury study have shown that penetrating lesions, specifically those localized to the prefrontal cortex, are associated with aggressive behavior in veterans. (Grafman et al., 1996) Genetic analysis of a subset of Vietnam Head Injury study participants showed that aggressive behavior was associated with monoamine oxidase A allele type in those with non-pre-frontal penetrating TBI. The association between genotype and aggressive behavior was not present in those with prefrontal cortex injuries. (Pardini et al., 2011)

RISK FACTORS FOR AGGRESSIVE BEHAVIOR AFTER TBI

Correlates of aggressive behavior in mixed severity TBI groups

Correlates of aggressive behavior have been examined using self-report scales and also using real-world consequences of aggressive behavior. Researchers have examined pre-injury and post-injury factors, and injury characteristics. Demographic factors, prior aggressive behavior, substance misuse, and psychological conditions are associated with aggressive behavior, but associative data cannot determine causation. While the literature shows those with more severe injuries tend to have more severe symptoms, the studies described here do not consistently show a correlation between prevalence or severity of aggressive behavior and injury characteristics related to severity.

Three relevant studies were found that examined correlates of aggressive behavior using self-report scales. In the study by Tateno et al. (2003), 89 civilians diagnosed with TBI (57% mTBI, 22% moderate, 22% severe TBI) were assessed within 6 months of injury. Those classified as belonging to the aggressive group had OAS scores of 3 or above and four episodes of significant aggressive behavior since injury. There was no difference in Glasgow Coma Scale scores (GCS) between the aggressive group and the non-aggressive group, but the aggressive group had a lower rate of diffuse lesion injuries and a higher rate of frontal lobe lesion injuries. (Tateno et al., 2003) Pre-injury factors associated with post-injury aggressive behavior were history of alcohol abuse, drug abuse, or mood disorder, or legal intervention for aggressive behavior prior to injury. Current depression symptoms, anxiety symptoms, and low Social Functioning Exam scores were also associated with aggressive behavior.

In a group of 67 civilians with TBI of varied severity (60% mild TBI, mean GCS score 12.2), Rao et al. (2009) aggressive behavior was not associated with injury severity (as measured

by duration of LOC) or neuropsychological test results. (Rao et al., 2009) Aggressive behavior was instead associated with diagnosis of new-onset major depression due to general medical condition (TBI), low post-injury social functioning, and post-injury dependence on others for activities of daily living.

A study of U.S. service members during Operation Enduring Freedom and Operation Iraqi Freedom (OEF/OIF) did not find evidence of a relationship between aggression scores and injury characteristics. Lange et al. divided 83 medically evacuated service members three groups based on TBI characteristics: uncomplicated mild, complicated mild, or moderate TBI. Complicated mTBI was defined as meeting PTA and LOC criteria for mTBI and having an intracranial abnormality visible by CT or magnetic resonance imaging (MRI) conducted within days of injury. Overall, measurements of psychopathology on the Personality Assessment Inventory (PAI) were similar between the severity groups. (Lange et al., 2012) Aggression subscores on the PAI did not differ between the groups based on an analysis of variance and an analysis of the distribution of individuals with elevated scores, although a pairwise comparison showed that scores were higher in the group with uncomplicated mTBI than the group with complicated mTBI.

Correlates of aggressive behavior after moderate and severe TBI

A variety of pre-injury, injury-related, and post-injury factors are associated with aggressive behavior after moderate and severe TBI. Three relevant studies were found: one that used self-report behavioral measures, one that used a clinician-rated scale, and one that used self-reported arrests as a primary outcome.

A recent prospective cohort study by Finnanger, et al. followed 67 individuals with moderate and severe TBI history, and compared them to uninjured controls. At 2-5 years post-injury, the individuals with TBI had higher scores on a self-report aggression scale. (Finnanger et al., 2015) A correlation analysis showed younger age at injury and depression symptoms during the first year after injury were correlated with a self-report scale that included aggression items.

The study by Sabaz et al. with 507 individuals with severe TBI participating in an outpatient rehabilitation program evaluated correlates of challenging behavior. Challenging behavior was defined as aggression, inappropriate sexual behavior (ISB), perseveration, wandering/ absconding, inappropriate social behavior, or adynamia. In a multivariate analysis, challenging behaviors were associated with poor psychosocial reintegration, severity of current mental health problems, and preinjury alcohol abuse. In pairwise analyses, higher levels of disability, longer duration of PTA, current alcohol misuse, and pre-injury psychiatric disturbance were also associated with challenging behaviors. Characteristics correlated with aggressive behavior specifically were not reported comprehensively, but available data showed that longer duration of PTA and pre-injury psychiatric disturbance were associated with aggressive behavior. (Sabaz et al., 2014)

One consequence of aggressive behavior can be criminal arrest. A prospective cohort study by Elbogen, et al. of several thousand civilians with moderate or severe TBI followed one to five years post-injury (N = 6315 for 1 year; N = 2690 for 5 years) showed that arrest was associated with a number of factors, according to Chi-square analysis. (Elbogen et al., 2014) Pre-injury factors included male gender, unmarried status, age under 25 years, no high school

education, pre-injury felony, pre-injury drug and alcohol misuse, and pre-injury special education. Other factors associated with arrest were violent cause of TBI, severe injury (i.e., LOC > 24 hours), and above-median motor function. In the multiple regression model, similar results were observed, except pre-injury special education was not significantly correlated with TBI, and being out of work prior to TBI was correlated in the 1 year follow-up data model. Interpretation of these data are limited by the fact that arrest can occur for reasons unrelated to aggressive behavior, and arrest is influenced by societal, environmental, and economic factors not considered in the study.

Prevalence and correlates of inappropriate sexual behavior after moderate and severe TBI

ISBs can be aggressive, but also can be the result of disinhibition. A research team in Australia has investigated ISBs in patients with severe TBI as they relate to other antisocial behaviors, functional outcomes, and other variables.

A retrospective study by Simpson et al. examined records from a rehabilitation unit that provided long-term inpatient and follow-up care for those with moderate and severe TBI. The total patient population included 445 individuals with TBI (severity not reported), and staff members identified 29 individuals who had committed ISBs. A total of 128 ISBs were documented in patient records, with four subjects accounting for a majority. The most common ISB was frotteurism (rubbing, 52 offenses), while other behaviors ranged from exhibitionism (29 offenses) to overt sexual aggression (12 offenses). Those who had a committed an ISB had more severe injuries than the rest of the patient population (post-traumatic amnesia 84 days compared to 49 days on average). (Simpson et al., 1999) The authors cautioned against over-interpreting these results due to the fact that the study population was drawn from the most severely injured persons, and the number of persons displaying ISBs was much smaller than the patient population (6.5% of patients met criteria for this study). In a follow-up case-control study by the same authors, a subset of cases who exhibited ISBs (n = 25) were matched with controls with TBI but who did not exhibit ISBs (n = 25). (Simpson et al., 2001) Social, radiologic, and medical factors (including radiologic findings) were examined to determine the correlates of ISBs. A global risk factor outcome was defined as having one or more of: substance abuse, employment difficulties, nonsexual criminal behavior, or psychiatric/ emotional disturbance. Factors that showed a significant association with ISBs were pre-injury unemployment, post-injury global risk factor, and several specific post-injury social variables, including: failure to return to work, substance abuse, and nonsexual criminal behavior. No medical or radiologic factors were associated with ISBs. Cases with ISBs also showed statistically significant neuropsychological deficits in planning, problem solving, and concept formation as compared to TBI controls.

A more recent cross-sectional study by Simpson et al. investigated incidents of ISBs (identified with subscale of Overt Behavior Scale) among 507 patients with severe TBI in Australia. Prevalence for ISB within the last 3 months was 8.9% (n = 45), according to clinician reports. ISBs included sexual talk, non-genital touching, self-exposure, public masturbation, genital touching, and sexual coercion. Verbal aggression, inappropriate social behavior, or other challenging behaviors accompanied ISB in 96% of cases. (Simpson et al., 2013) The subset of individuals exhibiting any inappropriate sexual actions (n = 21) had more severe injuries and higher care needs than individuals exhibiting inappropriate sexual talk only (n = 24). An article by Sabaz et al. with this same cohort showed that longer duration of PTA was associated with ISBs. (Sabaz et al., 2014)

These studies are limited to inpatient rehabilitation patients, and may not be applicable to other individuals with TBI. In addition, data on individuals with mild or moderate TBI were not included.

IRRITABILITY AND AGGRESSION IN NON-CLINICAL POPULATIONS

Irritability and aggression occur in the absence of TBI. Any association between aggressive behavior and TBI can be more clearly understood in comparison to associations between aggressive behavior and other medical and psychosocial factors. Such an analysis requires the inclusion of individuals without TBI history in the study population. The studies described in the above sections included individuals selected for positive TBI status. The below studies report on irritability, aggression, or anger in populations of individuals not selected based on TBI status. Data from military, veteran, and civilian populations are discussed.

Irritability, anger, and TBI status in military and veteran populations

Two studies present data regarding irritability or anger in military and veteran populations with and without TBI history. Assessing the incidence of irritability and aggression in military and veteran populations is complicated by deployment-related psychological trauma, including posttraumatic stress disorder, depression, and anxiety. (Galloway et al., 2012; Maguen et al., 2012) A survey of 2525 soldiers conducted three to four months after returning from deployment showed that those with no injuries reported irritability at a rate of 24.7%. Those with non-head injuries reported irritability at a rate of 36.8%. (Hoge et al., 2008) Among those with deployment-related TBI, the same survey documented irritability in 56.8% of those who experienced injury with LOC and 47.6% of those who experienced injury with no LOC. Deployment medical records of 907 soldiers who reported experiencing TBI during deployment at the post-deployment health assessment showed that 25.5% had irritability immediately after injury. (Terrio et al., 2009)

Feelings of anger have also been investigated in individuals with TBI history. Bailie, et al. conducted a study of military personnel with and without TBI history (more than 90% of TBIs were mild). Those reporting TBI history had higher scores on feelings of anger, personality traits relating to anger, and incidents of anger expression (aggression), and had lower scores on anger control. (Bailie et al., 2015) No differences in anger outcomes were observed between the mild and moderate/severe TBI groups. Of those with TBI history, 37% had three or more abnormal anger sub-scores, as compared to 13% of controls without TBI. Time since injury was correlated with reduced symptoms. Similarly, in a survey of driving difficulties, more than 80% of 134 OEF/OIF veterans (65% of whom had a TBI diagnosis) identified anger and impatience as a driving difficulty. (Lew et al., 2011) They experienced these feelings more often after deployment than before. However, neither of these results were adjusted for PTSD, which is a major correlate for aggression, as discussed below. (Elbogen et al., 2010b)

Correlates of anger, aggression, violence, and arrest in military and veteran populations

Studies of military and veteran populations have examined the correlates of violence and arrest. A literature review examined correlates of intimate partner violence and general violence among veterans, and did not find TBI status to be a major factor. (Elbogen et al., 2010a) Factors associated with intimate partner violence or general violence and aggression among veterans

included younger age, pre-deployment violence and criminal conduct, history of childhood abuse or neglect, PTSD diagnosis, substance abuse, depression symptoms, unemployment, lower socioeconomic status and lower income, and some studies found an association with combat exposure or combat trauma. Being a current victim of domestic violence was associated with perpetrating violence in several studies. (Elbogen et al., 2010a) In four studies of aggression, violence, or arrest in military/veteran populations published since this review, the primary correlates of anger and aggression did not include TBI status. PTSD, substance misuse, and history of violent behavior were found to be associated with violence and arrest in multiple studies.

In an exploratory study by Elbogen, et al. 676 OEF/OIF veterans (22% had experienced TBI during deployment) provided history information and completed an anger and hostility questionnaire. (Elbogen et al., 2010b) TBI history was only correlated with the three aggression-related outcomes (difficulty managing anger, aggressive impulses, and problems controlling violence) in the bivariate analysis, but was not correlated with these outcomes in the multivariate analysis. In contrast, PTSD/hyperarousal symptoms were the main correlate for all three of these outcomes in the multivariate analysis. (Elbogen et al., 2010b) These data suggest that TBI status may be a factor, but does not solely predict the incidence of anger and aggressive behavior in the post-deployed military/veteran population.

Three large studies of military and veteran populations published in the last 4 years are notable for findings related to aggression. A recent publication from the Army Study to Assess Risk and Resilience in Servicemembers (Army STARRS) project examined variables associated with a major non-familial violent crime among US soldiers. An administrative database containing almost one million soldiers was examined, and 5,771 cases of major physical violent crime (murder-manslaughter, kidnapping, aggravated arson, aggravated assault, robbery) were found. (Rosellini et al., 2015) A predictive model was constructed using 446 variables from the Historical Administrative Data System (HADS). TBI history was not predictive of major violent crime in the final models, which included 112 variables for men and 81 for women. In this study, major predictors of violent crime for men were less than high school education, not currently deployed, suicide attempt in the past year, and months deployed in unit of senior enlisted rank E5-E9. For women, major predictors of violent crime were junior enlisted rank, perpetrator of verbal violence in the past year, 6 or more days in the hospital for stressors/adversity in the past year, and hospitalization for depressive psychosis within the past year.

Two studies published in 2012 provide information on violence, arrest, and military populations: one on US service members, and one on US veterans. Gallaway et al. examined survey data from 6,128 active duty soldiers. Physical aggression was divided into minor (e.g., “slapped someone”) and severe (e.g., “punched/hit someone with something”) aggression. In a linear regression model, factors most strongly associated with minor physical aggression after adjustment for demographic factors included: lower education, lower enlisted rank, high combat intensity, history of or current alcohol misuse, prior history of physical altercation with significant other, and a history of depression. Significant predictors of serious physical aggression were similar, except history of depression had a lower effect size. TBI status was not significantly associated with minor physical aggression, but was significantly associated with severe physical aggression, although with a small effect size. (Gallaway et al., 2012) Elbogen et al. examined predictors for arrest in a survey of 1,388 OEF/OIF veterans. In a multivariable

analysis, the variables associated with arrest were: probable PTSD with high irritability, male gender, lower age, single status, lower education level, having witnessed domestic conflict, current substance misuse, and history of previous arrests. (Elbogen et al., 2012) Probable TBI was not associated with arrest in the logistic regression analysis. These studies suggest the most robust predictors of aggressive behavior and criminal behavior among veterans and returning service members are pre-deployment factors (especially history of aggressive behavior), combat trauma, PTSD symptoms, substance misuse. TBI was not consistently found to be predictive of aggressive behavior.

Two studies that did not consider TBI status confirmed that PTSD, combat or other trauma, alcohol misuse, and pre-deployment factors are associated with violent behavior. In an early study by Beckham et al. of U.S. Vietnam veterans, PTSD severity, combat exposure, and low socioeconomic status were associated with interpersonal violence. (Beckham et al., 1997) In a UK study of armed service personnel who had been deployed to Iraq, the strongest predictors of violence post-deployment were: reporting four or more trauma events, PTSD symptoms, heavy drinking, and pre-enlistment antisocial behavior. (Macmanus et al., 2012) Male gender was associated with aggression-related outcomes in this study and others. (Elbogen et al., 2012; Elbogen et al., 2014; Gallaway et al., 2012)

An early study by Ommaya et al. of military discharges after TBI found that service members with mild TBI history were 1.8 times more likely to be discharged for behavior, and 2.7 times more likely to be discharged for a criminal conviction, compared to the general service member population. (Ommaya et al., 1996) Reasons for behavioral discharge were not provided. This study did not control for co-morbid disorders or pre-morbid or personality factors that might affect risk of TBI and risk of criminal behavior. Risk of behavioral and criminal discharge was not elevated for individuals with moderate and severe TBI, who were much more likely to be discharged for medical reasons compared to the mild TBI group or the whole service member population. This study and the 2012 study by Elbogen et al, where arrest was the primary outcome, are limited by the fact that arrest and military discharge can be unrelated to aggressive behavior.

Correlates of physical aggression and criminal behavior in civilian populations

A number of studies have established that TBI history is more common in populations recruited from jails and prisons, and among those previously convicted of crimes, than in the general population. (Farrer & Hedges, 2011; Schofield et al., 2006; Shiroma et al., 2012) A recent retrospective cohort study examined the relationship between TBI history and criminality in Western Australia. Individuals with TBI were identified from hospital records, and matched with community controls or sibling controls in two separate Cox regression analyses. Both analyses controlled for drug or alcohol abuse, mental illness, Aboriginality, socioeconomic disadvantage, and adjusting for year of birth. In the analysis with community controls, results from 7694 cases showed a 58% and 73% increased risk of criminal conviction for those with TBI history in males and females, respectively. In the sibling analysis (2397 cases), risk of conviction for men with TBI history was 69% higher than for controls without TBI history, but for women with TBI history, there was no increase in risk. When only violent convictions were examined, the results were similar. (Schofield et al., 2015) No data were provided regarding how TBI severity or other injury characteristics affected risk of criminal conviction.

TREATMENT OF IRRITABILITY AND AGGRESSIVE BEHAVIOR AFTER TBI

Published clinical recommendations and guidelines

Clinical practice guidelines for moderate and severe TBI do not offer recommendations regarding non-pharmacological behavioral health treatment. The DoD and VA Clinical Practice Guidelines for mTBI (2009) acknowledge aggression, irritability, impulsivity, and socially inappropriate behavior as a possible sequelae of mTBI and suggest screening for psychiatric symptoms and co-morbid disorders. (Department of Defense & Department of Veterans Affairs, 2009) Regardless of comorbidities, patient education regarding symptoms, expectation of recovery, and stress management is recommended. The guidelines recommend appropriate, individualized psychotherapeutic and pharmacological treatment for psychiatric comorbidities. The guidelines specifically recommend considering a several week trial of a pharmacologic agent for behavioral symptoms, with anti-convulsants and selective serotonin reuptake inhibitors (SSRIs) being well-supported by evidence. SSRIs are supported as the pharmacological treatment of choice for depressive symptoms, irritability and poor frustration tolerance in the mTBI population, but no specific treatment recommendations are offered for aggressive behavior. (Department of Defense & Department of Veterans Affairs, 2009).

The DoD and VA Clinical Practice Guidelines for PTSD provide specific recommendations regarding managing anger and aggression. (Department of Defense & Department of Veterans Affairs, 2010; Taft et al., 2012) While many individuals with TBI do not have PTSD, these recommendations may be helpful for providers. The nine recommendations include five non-pharmacological recommendations, including promoting participation in enjoyable activities, and four recommendations relevant to pharmacological management, including avoiding stimulants.

Pharmacological management

A number of pharmacological agents have been studied for management of aggressive behavior in the TBI population. A 2016 publication of the French Society of Physical Medicine and Rehabilitation (SOFMER) included a systematic review and expert panel recommendations regarding drugs for behavioral disorders after TBI. The authors identified 16 systematic reviews or controlled studies and 73 studies with other designs. (Plantier et al., 2016) Evidence regarding beta-blockers, neuroleptics, antipsychotics, antidepressants, antiepileptic drugs, benzodiazepines, amantadine, and other drugs was presented. The authors noted that the level of evidence available was generally low. For irritability and aggressiveness, the evidence supporting beta-blockers and mood stabilizing antiepileptic agents was stronger than for other classes of drugs. The authors recommended considering neuroleptics and antidepressants as second-line treatments.

A 2009 review (Chew & Zafonte, 2009) describes evidence regarding the use of beta-blockers, neuroleptics, anticonvulsants, antidepressants, neurostimulants, amantadine, and lithium for agitation and aggression. Beta-blockers and neuroleptics are limited by intolerance and adverse effects. The review concluded that anticonvulsants demonstrate promise, and limited data suggests lithium and amantadine may be beneficial. Insufficient evidence was available to assess the benefit of antidepressants for agitation and aggression after TBI, although the tricyclic antidepressant amitriptyline has shown benefit in one small study. (Chew & Zafonte, 2009)

In 2006, an expert panel published guidelines for the pharmacological management of neurobehavioral TBI sequelae. (Warden et al., 2006) For aggressive behavior after TBI, there was insufficient evidence to develop a treatment standard, but beta-blockers including propranolol and pindolol were recommended as a guideline based on nine published studies. A 2004 systematic review of pharmacologic interventions for TBI, which found limited evidence for the effectiveness of anti-depressants, anti-convulsants, and high-dose beta blockers for treating aggressive behavior following TBI. (Deb & Crownshaw, 2004)

Amantadine is a psychostimulant and a dopaminergic agent, and has been investigated to improve alertness and decrease irritability after TBI. A 2015 systematic review by Stelmaschuk et al. evaluated several studies of amantadine for moderate to severe traumatic brain injury. (Stelmaschuk et al., 2015) Three double-blind, randomized, controlled human trials were found. Results from two studies showed that amantadine can improve disability ratings scale scores. (Giacino et al., 2012; Meythaler et al., 2002) A third trial found that amantadine had a positive effect in irritability scores. (Hammond et al., 2014) However, side effects of amantadine can include agitation and aggression, (Stelmaschuk et al., 2015) so observed improvements in irritability may have been due to indirect effects or particular features of the participant population. A multi-center trial on amantadine for irritability published after the systematic review found no significant differences between the amantadine and placebo groups at treatment midpoint or endpoint. (Hammond et al., 2015)

Non-pharmacological management

Little evidence is available regarding non-pharmacological interventions for aggression and irritability following moderate and severe TBI. A 2016 publication of SOFMER included a systematic review and expert panel recommendations on interventions for psychological and behavioral disorders after TBI found 93 relevant articles, the majority of which were the lowest level of evidence, and none of which provided the highest level of evidence. (Wiart et al., 2016) The authors recommended, based on expert opinion and limited evidence, that non-pharmacological treatment for behavioral disturbances should be used as a first-line treatment. The expert panel also recommended a coordinated approach to care that considers the medical, social, and environmental needs of the individual. More articles (17 studies and nine reviews) discussed cognitive-behavioral therapy (CBT) than any other intervention, and at least eight of those addressed irritability, anger, or aggression outcomes. Based on this evidence and expert opinion, the authors recommended CBT for patients with irritability and bouts of anger. Work published after the 2012 cutoff date of this systematic review also supports the use and further study of CBT after TBI. (Aboulafia-Brakha et al., 2013)

Interventions in community settings for behavioral disorders after brain injury were reviewed by SOFMER in 2015, and the expert panel identified two studies with interventions and outcomes relevant to irritability and aggression. (Luaute et al., 2015) A randomized controlled trial with 47 individuals with TBI or stroke history found that an 8-week individualized behavioral modification program reduced the frequency of disruptive or aggressive behaviors at a 3-month follow-up assessment, compared to a control group without the program. (Carnevale et al., 2006) The other study was a feasibility trial of a videoconferencing training program with 15 caregivers. The training included six educational sessions on topics including “Changes in language and social communication” and “Changes in emotions and behavior.” The participants indicated satisfaction with the program and reported

using the information gained, but data regarding irritable or aggressive behaviors was not collected. (Sander et al., 2009)

Previous research has shown that irritability after TBI exists within relationships as well as individuals. Improving interpersonal interactions may reduce triggers for negative and irritable responses. Researchers studied qualitative data derived from the transcripts of focus groups that included individuals with TBI history, their spouses, mental health professionals, and researchers. The goal was to determine the impact of spousal interactions on irritability and the impact of TBI on marital relationships. Data showed that spouses can trigger irritability in individuals with TBI history, and vice versa. The authors recommended a comprehensive approach that considers the family unit when treating problematic behavior in individuals with TBI history. (Hammond et al., 2012) A small pilot study of an anger management training program that included significant others and patients with moderate or severe TBI demonstrated significant improvements in self-reported anger and aggression scores, as well as significant-other reported anger expression scores. (Hart et al., 2012)

An early cognitive rehabilitation study by Salazar et al. examined the effect of two treatments on self-reported behavioral outcomes. Active-duty military personnel with moderate or severe TBI history (N = 120) were assessed before treatment and 1 year after baseline. No differences between the cognitive rehabilitation intervention groups were observed in aggression, belligerence, or antisocial behavior. (Salazar et al., 2000)

CONCLUSION

This research review summarizes recent and important developments in the scientific literature on irritability, aggressive behavior, and TBI. Studies have shown that irritability is a TBI symptom that occurs in a minority of individuals with TBI of any severity, and persists in a subset.

Data consistently show that PTSD diagnosis or symptoms, substance abuse, history of aggressive behavior, and other factors are more predictive of aggressive behavior than TBI history. Among individuals with TBI history, aggressive behavior is associated with pre-injury factors, injury characteristics, and post-injury factors. Pre-existing conditions including substance abuse, prior aggressive behavior, and psychiatric illness increase the likelihood of post-injury aggressive behavior. (Tateno et al., 2003) Frontal lobe injury, especially from penetrating injury, is associated with aggressive and antisocial behavior. (Brower & Price, 2001) Data are inconsistent regarding the relationship between injury severity and aggressive behavior, one large study showed an association between severe TBI and criminal arrest. (Elbogen et al., 2014) Post-injury factors related to aggressive behavior include current depression and anxiety symptoms or diagnoses, low social functioning, and dependence on others for activities of daily living. (Rao et al., 2009; Tateno et al., 2003) Post-TBI criminal arrest is linked to pre-TBI risk factors such as demographic factors, prior arrest, and substance abuse, mirroring those risk factors of the non-TBI population. (Elbogen et al., 2012) These data are correlative; there is no evidence that TBI causes aggressive behavior.

The conclusions presented here are consistent with those of a 2009 systematic review on long-term psychiatric outcomes after TBI that was conducted by a committee of experts. The committee concluded: “there is sufficient evidence of an association between TBI and

subsequent development of aggressive behaviors. Additional evidence that aggression is associated with TBI primarily when frontal cortical lesions are sustained is consistent with a large literature associating frontal lobe damage with loss of behavioral control.” (Hesdorffer et al., 2009)

There are significant limitations to the literature on aggression, irritability, and TBI. Definitions and assessment metrics of TBI, irritability, anger, and aggression vary across studies, limiting comparability. Pre-morbid data regarding personality and neurobehavioral characteristics are limited and influenced by recall bias. Much of the data relies on self-report or family-report, and the frequency and severity of behaviors is not described in detail. Some studies of individuals with TBI history have small sample sizes. Findings from studies with civilian samples may not easily transfer to military or veteran populations. Military populations with mTBI history have higher rates of comorbid PTSD and other psychiatric conditions than civilian populations of individuals with mTBI. (Bryant et al., 2010; Schneiderman et al., 2008) Studies on frontal lobe injury are limited by incomplete reporting on pre-morbid and co-morbid risk factors for aggressive behavior. Studies of arrest and military discharge are limited by the fact that these outcomes can be unrelated to aggressive behavior and may be influenced by societal, environmental, and economic factors.

Future studies that use consistent definitions, family and clinician reports of symptoms, and a longitudinal design with pre-injury baseline assessments would address these limitations. Using common data elements will enable better comparisons of treatments, and meta-analyses on prevalence and treatment questions. Continued research on genetic, imaging, and fluid biomarkers will further understanding of aggressive behavior in individuals with TBI and may enable prediction of risk of aggressive behavior and provide new information on best mitigation strategies. Intervention studies focused on psychological health outcomes will further advance tools for helping individuals with TBI history coping with irritability and anger issues.

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