Review

Affective, neurocognitive and psychosocial disorders associated with traumatic brain injury and post-traumatic epilepsy

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ABSTRACT

Survivors of traumatic brain injury (TBI) often develop chronic neurological, neurocognitive, psychological, and psychosocial deficits that can have a profound impact on an individual's wellbeing and quality of life. TBI is also a common cause of acquired epilepsy, which is itself associated with significant behavioral morbidity. This review considers the clinical and preclinical evidence that post-traumatic epilepsy (PTE) acts as a 'second-hit' insult to worsen chronic behavioral outcomes for brain-injured patients, across the domains of emotional, cognitive, and psychosocial functioning. Surprisingly, few well-designed studies have specifically examined the relationship between seizures and behavioral outcomes after TBI. The complex mechanisms underlying these comorbidities remain incompletely understood, although many of the biological processes that precipitate seizure occurrence and epileptogenesis may also contribute to the development of chronic behavioral deficits. Further, the relationship between PTE and behavioral dysfunction is increasingly recognized to be a bidirectional one, whereby premorbid conditions are a risk factor for PTE. Clinical studies in this arena are often challenged by the confounding effects of anti-seizure medications, while preclinical studies have rarely examined an adequately extended time course to fully capture the time course of epilepsy development after a TBI. To drive the field forward towards improved treatment strategies, it is imperative that both seizures and neurobehavioral outcomes are assessed in parallel after TBI, both in patient populations and preclinical models.

1. Introduction

Traumatic brain injury (TBI) is a major cause of morbidity and mortality worldwide. For many survivors, chronic consequences of injury to sensorimotor and neurocognitive systems can range from mild neurological symptoms through to severe disability, and can be accompanied by significant psychosocial changes (Bhalerao et al., 2013; Emery et al., 2016). Together, these outcomes often have a profound impact on an individual's wellbeing and quality of life (QoL).

Post-traumatic epilepsy (PTE) is defined as one or more unprovoked seizures that occur at least a week after TBI, and has a variable incidence of 4–50% in TBI populations, with some of this variability attributed to injury severity (Verellen and Cavazos, 2014). PTE is one of the most common types of focal epilepsy, with trauma estimated to be

an etiological factor in up to 20% of acquired epilepsies in the general population (Agrawal et al., 2006; Piccenna et al., 2017). Risk factors for PTE include factors related to the injury itself (e.g. severity, intracerebral hemorrhage, penetrating injuries, early post-traumatic seizures), and factors related to the individual (e.g. age, family history of epilepsy, premorbid alcohol abuse or depression) (Piccenna et al., 2017; Verellen and Cavazos, 2014). Seizures experienced by people with PTE are typically focal onset seizures, most commonly originating from the temporal lobe, that may or may not secondarily generalize to tonic-clonic convulsive activity (Agrawal et al., 2006).

In the absence of a precipitating traumatic insult, seizure disorders such as epilepsy are well-known to be associated with significant behavioral dysfunction including depressive symptoms, memory deficits, personality changes, anxiety, and difficulties with social interactions

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(Quintas et al., 2012). These features can have a profoundly negative effect on an individual's wellbeing and perceived quality of life (Lehrner et al., 1999; Szemere and Jokeit, 2015), possibly more so than the seizures themselves (Boylan et al., 2004). Of note, the relationship between behavioral problems and seizures is a complex one, likely influenced by not only the recurrent seizure activity but also the medical treatments administered for seizure control, as well as social stigma and psychological impact of the diagnosis (Szemere and Jokeit, 2015). Further, despite the traditional view that behavioral problems are consequential to seizure disorders, this relationship is increasingly understood to be a complex and bidirectional one, whereby a higher prevalence of primary psychiatric disorders has repeatedly been observed in epilepsy patients even prior to the onset of seizures (Hesdorffer et al., 2012; Kanner et al., 2014; Salpekar, 2017)

The behavioral domains most commonly affected in patients with epilepsy are often also affected in patients following TBI. It is therefore reasonable to suspect that epilepsy as a consequence of TBI (i.e. PTE) confers an additional disability on an individual who has sustained a TBI to worsen behavioral comorbidities (Kolakowsky-Hayner et al., 2012). However, a surprising paucity of studies have examined this hypothesis. This review will discuss the clinical and preclinical literature of behavioral deficits that commonly manifest after both TBI and epilepsy, and highlight evidence suggesting (or rejecting) the hypothesis that PTE acts as a 'second-hit' insult to worsen chronic behavioral outcomes for TBI patients. For simplicity, symptoms are considered from the perspective of affective disorders, cognitive impairment, and social dysfunction, although there is obviously considerable overlap and interaction between these functional domains (Steiger and Jokeit, 2017).

2. Affective disorders

2.1. Affective disorders in people with TBI

Around 60% of people experience a psychiatric illness in the 12-months following a TBI, with affective disorders such as depression and anxiety the most common presentation (see (Ponsford, 2017) for a comprehensive recent review). A bidirectional relationship between TBI and affective disorders seems to exist, whereby in addition to the elevated rates of depression and anxiety after injury, the presence of pre-injury affective illness is a robust vulnerability factor for worse psychiatric and medical outcomes after a head injury (Jorge and Robinson, 2003; Ponsford, 2017). As such, the etiology of post-TBI affective disorder is likely best conceptualized as multifactorial; a product of both psychosocial and neurobiological factors.

After TBI, a psychological process of grief and adjustment can occur in response to sudden changes in personal circumstance caused by the injury (Claude Blais and Boisvert, 2005). Such psychosocial changes can be temporary or permanent, including physical and cognitive disabilities, disfigurement, un- or under-employment, physical and financial dependence on others, changed family roles, social isolation, challenges to personal identity (i.e., "*who am I now?*"), bereavement of others involved in the incident, and in some scenarios, forensic consequences. This difficult process can give rise to depression and anxiety in some people. Patients especially vulnerable to emotional maladjustment after TBI are those with a lower premorbid IQ, or with a coping style characterized by avoidance, worry, wishful thinking, self-blame, and drug/alcohol use (Anson and Ponsford, 2006).

The complex process of self-reflection and re-evaluation after TBI can be complicated by the neurobiological sequelae of the injury. Excessive fatigue may persist well into the sub-acute and chronic phases of neurological recovery (Ponsford, 2017), with the downstream effect of undermining a patient's cognitive capability to engage in the psychological process, and perpetuating lifestyle restrictions via the need for regular rest and avoidance of overstimulation. Neurobiological mechanisms linked to cognitive fatigue after TBI include pre-injury

relative hypocortisolaemia, which may sensitize the hypothalamic-pituitary-adrenal axis to development of persistent fatigue after stress (Chaudhuri and Behan, 2004), a reduced number of the hypothalamic neurons that produce the wake-promoting neuropeptide hypocretin (Baumann et al., 2009), and trauma to the vmPFC hub of cortico-striatal risk/reward decision-making networks (Pardini et al., 2010).

In humans, the neural underpinnings of elevated depression and anxiety after TBI are difficult to elucidate given the sheer heterogeneity in the mechanism and distribution of injuries; however structural and functional changes to emotion-regulating brain networks involving cortico-subcortical pathways between the prefrontal and mesial temporal regions provide a feasible organic account for emotional dysregulation in some cases (Jorge and Robinson, 2003). Of relevance to the potential shared mechanisms between affective disorder and epilepsy in TBI, anti-epileptic drugs such as sodium valproate and carbamazepine are routinely used to manage atypical affective symptoms seen after severe TBI such as aggression and agitation, although a strong evidence base for their use is lacking (Fleminger et al., 2006).

Cognitive deficits resulting from a TBI can also intersect with the development of an affective disorder. For instance, cognitive rigidity or 'concrete thinking' is a classic symptom of traumatic frontal lobe damage that undermines a patient's ability to think flexibly about their problems and reframe them in new or abstract ways (Whiting et al., 2017). Emotion-recognition difficulties form part of a suite of social cognition impairments sometimes seen after more serious cases of TBI (Babbage et al., 2011), which are particularly pertinent to psychosocial disability after TBI given that the ability to infer the mental states of those around us is crucial to maintaining social supports (Knox and Douglas, 2009). Perhaps counter-intuitively, more severe cognitive deficits may be somewhat of a protective factor against the development of post-TBI affective disorder (Jorge and Robinson, 2003). In part, this may be because some of the psychopathology underlying depression and anxiety relies on higher-order self-reflection and abstraction that may be beyond the intellectual capabilities of patients with diffuse or severe cognitive impairments. Patients may also be somewhat protected when their neuropsychological profile includes anosognosia i.e., a lack of insight into one's (cognitive) deficits. This 'blissful ignorance' can vanish should their insight grow; perhaps in the context of a failed return to work or other 'real life' proof of their deficits (Fleminger et al., 2003).

Patients with severe TBI, however, are not immune to neuropsychiatric disturbance. In a study of 120 patients with severe TBI and no psychiatric history, common behavioral features included apathy (42%), irritability (37%), dysphoria (29%), vegetative disturbances (27%), agitation/aggression (24%), and more rarely, anxiety (8%). These features were linked to older age of TBI patients, structural lesions on MRI, and a poor functional outcome (Ciurli et al., 2011). An acute inflammatory biomarker profile comprising elevated levels of Cerebral spinal fluid cytokine surface markers (sVCAM-1, sICAM-1, sFAS) predicted post-injury depression in a sample of people with moderate-to-severe TBI (n = 41) (Juengst et al., 2015), indicating the need for more investigation into the role of chronic inflammation in post-TBI affective disorders.

2.2. Affective disorders in people with epilepsy

Depressed mood is the most prominent psychiatric symptom of epilepsy (Tellez-Zenteno et al., 2007), and is often perceived by patients as more debilitating than the primary problem of unpredictable seizures (Boylan et al., 2004). Specifically, 1 in 2 people with epilepsy will also endure a clinically significant depressive disorder at some point in their lifetime (Rayner et al., 2016b), as opposed to 1 in 6 people from the healthy community (Statistics, A. B O, 2008). While there is often a process of psychological adjustment centered around the confronting loss of control that accompanies that sudden onset of seizures in adulthood (Velissaris et al., 2007), depression in epilepsy is not just a

'reaction' to psychosocial limitations imposed by seizures, like being unable to drive or work. Epilepsy has a far higher rate of depression than similarly disabling diseases (Ettinger et al., 2004), suggesting that there may be something intrinsic to the neurobiology of epilepsy or seizures that causes depressive symptoms. This notion of a shared neurobiological cause between depression and seizures is underscored by the longstanding observation that a bidirectional relationship exists between the two conditions. For example, patients with epilepsy are more likely to develop depression than people in the general population, whereas sufferers of unipolar depression are at 4- to 7-times greater risk of experiencing an unprovoked seizure (Kanner et al., 2014).

2.3. Neurocognitive network models of comorbid affective disorder in epilepsy

Mood and cognition are currently considered to be the emergent property of brain networks (Sporns, 2011), and epilepsy a neurological disease that causes seizures to propagate along and alter these same networks (Scheffer et al., 2017; Wilson and Baxendale, 2014). In particular, neuroimaging and behavioral research indicates that habitual seizures have a predilection for cognition-related brain networks known to be important to the pathogenesis of depressive symptoms (see (Rayner, 2017) for a review), such as the autobiographic memory network and the cognitive control network (Rayner et al., 2016a). Simultaneous EEG-fMRI shows that neurocognitive networks are often co-activated during epileptiform discharges (Pillay et al., 2013), altering their functioning and connectivity over time (Liao et al., 2011).

Dysfunction of cognition-related brain networks is thought to underlie the heterogeneous mix of cognitive, affective, and somatic symptoms that comprise unipolar depression. In epilepsy, cognitive network dysfunction is directly linked to depression in cases presenting with a cognitive phenotype of depressive disorder (Rayner et al., 2016b). Of the 25% of epilepsy patients meeting criteria for depressive disorder at any one time, initial evidence suggests that most (71%; base rate = 17%) have a phenotype characterized by cognitive symptoms such as subjective memory complaints, indecisiveness, poor concentration, and parasuicidal rumination; this cognitive phenotype of depression is associated with psychometric memory impairment, a profile that together implicates dysfunction in the autobiographic memory network and cognitive control network. The remaining 29% (base rate = 7%) present with a somatic or melancholic phenotype characterized by anhedonia, anxiety and vegetative symptoms like disturbed sleep and appetite, suggesting dysfunction in cortico-subcortical networks that subserve emotional and vegetative processing. These phenotypes are congruent with those found in other medical and psychiatric populations (Blazer et al., 1988; Haslam and Beck, 1993; Marijnissen et al., 2011), and add to a growing literature that different presentations of depression in epilepsy may indicate dysregulation of different brain networks (Lothe et al., 2008). In terms of potential biomarkers, framing both epilepsy and its affective phenotypes in terms of dysfunction in distinct cognitive networks (or 'biotypes') raises the possibility that affective disorder could be a primary feature of epileptogenesis in some cases.

2.4. Affective disorders in people with PTE – a call to researchers

Despite the well-established risk of mood disorder in the context of TBI and of epilepsy, there is little research looking into the prevalence, presentation, or mechanisms associated with affective disorder in people with PTE. In one rare attempt to delineate the presence of broad neuropsychiatric features in PTE versus TBI, Mazzini et al. (2003); n = 143 found that the ~20% patients who developed epilepsy after a TBI had a significantly higher incidence of personality disorders and disinhibited behavior than patients without PTE. They also showed more frequent and severe displays of emotional dysregulation such as

irritability, agitation, and aggression, which are often interpreted as atypical features of depressive and anxiety disorders in the brain-injured population. Despite no difference in the cognitive outcome of TBI patients with and without PTE in this sample, the PTE group also had a worse functional outcome a year after the injury, providing preliminary evidence that seizures could confer additional neuropsychiatric burden after TBI, with emotional dysregulation a potentially key determinant of psychosocial rehabilitation (Mazzini et al., 2003). Moving forwards, establishing the prevalence and phenotypic spectrum of affective disorder in PTE is a matter of priority. In addition to giving a sense of the scale of the problem, such information will provide clinicians with a clear guide regarding what specific affective symptoms to monitor for in this population, with better diagnosis leading to prompt management and better functional outcomes.

Once the prevalence and phenotypes of mood disorder in PTE is established, the search for biomarkers of PTE and depression may benefit from the neurocognitive network model of depressive symptoms currently applied to primary epilepsy. Although speculative, this approach is reasonable given that there is preliminary behavioral evidence that disruption to the autobiographic memory network and cognitive control networks are linked to depressive symptoms after TBI (Chamelian and Feinstein, 2006; Rapoport et al., 2005; Williams et al., 1998). Framing PTE and its affective comorbidities in terms of dysfunction in overlapping cognitive networks provides a neurobiological model of affective symptoms in humans that can be tested using behavioral and neuroimaging methodologies, and is in keeping with the gold standards for psychiatric research as outlined by the U.S.'s National Institute of Mental Health (Insel et al., 2010). In particular, the discovery of distinct neural patterns linked to different phenotypes (i.e., biotypes) can help zero in on disturbed region-specific neurotransmitter systems (Hamilton et al., 2011), which can provide a target for novel therapy models tailored to that phenotype. As per the goals of precision medicine, this has the potential for behavioral phenotypes to be used to better individualize treatment decisions around PTE and its psychiatric morbidities.

2.5. Animal models of TBI exhibit disturbed depression- and anxiety-like behaviors

Similar to the clinical evidence described above, many experimental studies of TBI report depressive-like phenotypes in injured rodents, and these are summarized in Table 1. These studies have been conducted in many different laboratories, and incorporate a wide variety of injury models, ages and species of subject, time of measurement after injury, injury frequency and severity and the reported outcome measures. Although there are also negative reports (see Table), the depressive phenotype would appear to be one of the most consistent and robust consequences of TBI.

The most common tasks used to assess depression-like behavior in rodents are the forced swim test (FST) (Porsolt et al., 1977), and the tail suspension test (TST) (Steru et al., 1985). In these tasks, animals are placed into an inescapable situation – either a tall cylinder of water, or hanging from a thin wire. Initially, the animals struggle vigorously to escape, but after some time, they stop struggling and adopt a passive posture. This is likened to behavioral despair, a core symptom of clinical depression in humans. The primary strength of these tests are that they are predictive of antidepressant actions – reducing the time spent 'immobile' is a feature of antidepressants (Porsolt et al., 1977). By extension, an animal that exhibits greater time immobile is said to exhibit a depressive-like phenotype. Another commonly used assessment of depressive-like behavior challenges the hedonistic drive of animals. This is frequently impaired in patients experiencing depression, who display anhedonia or reduced pleasure-seeking activities. In rodents, this can be assessed using the sucrose preference test (SPT), measured by presenting two water bottles, one with normal tap water and the other with sucrose or saccharin added (Klein et al., 2015). Most rodents

Table 1
Summary of studies examining depression-related behavior in rodent models of TBI. TBI was delivered to anaesthetised adult animals, unless otherwise stated. FST – Forced Swim Test, SPT –Sucrose preference test, TST – Tail Suspension Test, NSFT – Novelty Suppressed Feeding Test, CCI – Controlled Cortical Impact, FPI - Fluid Percussion Injury, GSK-3 – Glycogen synthase kinase 3, LiCl – Lithium chloride, DHEAS – Dehydroepiandrosterone, TSG-6 – Tumor necrosis factor stimulated gene 6.

Model	Citation	Species	Severity	Frequency	Test	Depression phenotype
Weight-drop	Milman, 2005	Mouse	Mild	Single	FST	Depression-like phenotype in TBI mice
	Shapira et al., 2007	Mouse	Mild	Single	FST	Depression-like phenotype in TBI, reversed by LiCl, GSK-3 inhibitor
	Tweedie, 2007	Mouse	Mild	Single	FST	Depression-like phenotype in TBI mice
	Milman, 2008	Mouse	Mild	Single	FST	Depression-like phenotype in TBI, improvement at 90 days with DHEAS treatment
	Lesniak, 2017	Mouse	Mild	Single	TST	Increased depression-like behaviour following TBI in LA mice
	Kosari-Nasab, 2018	Mouse	Mild	Single	FST, SPT	Depression-like phenotype in TBI mice
	Nichols, 2016	Mouse	Mild	Repeated	FST	No phenotype in TBI mice
	Liu, 2017	Mouse	Mild	Repeated	FST	No phenotype in TBI mice
	Schwarzbold, 2010	Mouse	Variable	Single	FST	No phenotype in TBI mice
	Corrigan, 2017	Rat	Mild	Repeated	FST	Depression-like phenotype in TBI rats
	Tan et al., 2015	Rat	Not classified	Single	FST, SPT	Depression-like phenotype in TBI rats, reduced by amantadine
CCI	Yang, 2015	Mouse	Mild	Repeated	FST	No phenotype in TBI mice
	Wang, 2011	Mouse	Moderate	Single	FST	No phenotype in TBI mice
	Washington et al., 2012	Mouse	Variable	Single	FST	Depression-like phenotype in TBI mice
	Tucker et al., 2017	Mouse	Variable	Single	SPT, FST	No phenotype in TBI mice
	Watanabe et al., 2013	Mouse	Not classified	Single	FST, NSFT	Depression-like phenotype in TBI mice, improved by TSG-6 (anti-inflammatory) treatment
	Petraglia et al., 2014	Mouse (conscious)	Not classified	Repeated	FST,TST	Depression-like phenotype in TBI mice
	Klemenhagen et al., 2013	Mouse	Not classified	Repeated	TST, SPT	Depression-like phenotype in TBI mice
	Cope et al., 2011	Rat	Not classified	Single	SPT	Depression-like phenotype in TBI rats, improved by zinc supplementation
	Cope, 2012	Rat	Not classified	Single	SPT	Depression-like phenotype in TBI rats
	Darkazalli et al., 2016	Rat	Not classified	Single	SPT	Depression-like phenotype in TBI rats, reversed with stem cell treatment
FPI	Shultz et al., 2012a	Rat	Mild	Single	FST	No phenotype in TBI rats
	Shultz et al., 2012b	Rat	Mild	Repeated	FST	Depression-like phenotype in TBI rats
	Webster et al., 2015	Rat	Mild	Repeated	FST	No phenotype in TBI rats
	Mychasiuk et al., 2014a, 2014b	Rat (juvenile)	Mild	Single	FST	Depression-like phenotype in TBI rats
	Jones et al., 2008	Rat	Moderate	Single	FST, SPT	No phenotype in TBI rats
	Rowe, 2016	Rat (varying ages)	Moderate	Single	FST	No phenotype in TBI rats
Blast injury	Reiner, 2015	Mouse	Mild	Single	TST	Depression-like phenotype in TBI mice, reversed by SMM-189 - CB2 receptor inverse agonist
	Heldt, 2014	Mouse	Variable	Single	TST	Depression-like phenotype in 60psi injured vs 30psi injured rats

will strongly favor the sweetened drink, presumably deriving pleasure from this solution. An animal who does not prefer the sucrose therefore exhibits anhedonia, a hallmark depressive symptom. Other tests of depression-like behaviors and physiological markers of depression can also be studied (Mazarati et al., n.d., accepted for publication), but these have not been frequently measured in models of TBI.

A variety of different experimental models of TBI have been employed to investigate depressive-like behaviors in this context. These include the weight-drop model (also referred to as an impact-acceleration model), the controlled cortical impact model (CCI; involving focal damage to the cortical surface), fluid-percussion injury (FPI; causing both focal damage and diffuse axonal injury), and blast injury (of high relevance for military personnel; see Table 1). Whilst some report no change in injured animals, all of these models have been shown to cause behavioral despair and anhedonia in rodents. The reproducibility and robustness of the depressive phenotype facilitates the study of biological mechanisms responsible for generating these behaviors, and allows investigation of new therapeutics. On this note, several pharmacological approaches have demonstrated improvements in TBI-associated depression-like behaviors. For example, depression behavior caused by experimental TBI is reportedly reduced by such diverse treatments as glycogen synthase kinase 3 (GSK-3) inhibition (Shapira et al., 2007), the antiviral and antiparkinsonian drug amantadine (Tan et al., 2015), anti-inflammatory agents (Watanabe et al., 2013), zinc supplementation (Cope et al., 2011), a CB2cannabinoid receptor inverse agonist (Reiner et al., 2014) and stem cell transplants (Darkazalli et al., 2016), although an early meta-analysis failed to find evidence of efficacy against depression-like behaviors (Wheaton et al., 2011). To date, no studies have assessed whether depression-like

behaviors occurring after TBI can be reduced by clinically used antidepressants, and this would be a valuable study to demonstrate the predictive validity of this phenotype.

Although less commonly reported, several studies also document the presence of anxiety-like behaviors in models of TBI. These behaviors can also be triggered in both rats and mice by weight drop injury, CCI, FPI, and blast injury (Table 2). The most frequently utilized tests of anxiety take advantage of the natural instincts of rodents to explore their surroundings contrasted against their fear of open, exposed spaces. Equipment such as the Elevated Plus Maze, the Elevated Zero Maze, the Open Field or the Light-Dark Box are all commonly used as valid assessments of state anxiety, and have been used to explore anxiety-like behaviors following TBI (.

The anxiety phenotype is less consistently observed following TBI, compared to depression-like behaviors. While the majority of studies do report increases in anxiety-like behavior, particularly following FPI or blast injury, other reports show reduced levels of anxiety in injured rodents. Some authors conclude that this represents increased risk taking, or increased exploration, as opposed to an anxiolytic effect of TBI (Petraglia et al., 2014). While this interpretation may be accurate, other assessments should be adopted to confirm this. One important study used a 'hyperemotionality score' to assess anxiety and depression-like phenotype. The scoring consisted of a composite score combining the startle response, struggling response and fighting response, and this was elevated in rats suffering a weight drop injury (Pandey et al., 2009). Treatment with escitalopram, a selective serotonin reuptake inhibitor commonly prescribed for mood disorders, was able to normalize the aberrant behaviors in this model, providing some evidence of predictive validity for these outcomes.

Table 2
Summary of studies examining anxiety-related behavior in rodent models of TBI. TBI was delivered to anaesthetised adult animals, unless otherwise stated. EZM – Elevated Zero Maze, EPM – Elevated Plus Maze, OFT – Open Field Test, LDB – Light Dark Box, CCI – Controlled Cortical Impact, FPI - Fluid Percussion Injury.

Model	Citation	Species	Severity	Frequency	Test	Anxiety phenotype
Weight drop	Kosari-Nasab, 2018	Mouse	Mild	Single	EZM	Increased anxiety in TBI mice
	Nichols, 2016	Mouse	Mild	Variable	EPM	No effect of TBI
	Liu, 2017	Mouse	Mild	Repeated	EPM, OFT	Reduced anxiety in TBI mice, mitigated by enrichment
	Schwarzbold, 2010	Mouse	Variable	Single	EPM	Increased anxiety following mild TBI (but not moderate or severe)
	Siopi, 2012	Mouse	Not classified	Single	EPM,EZM	No effect of TBI
	Corrigan, 2017	Rat	Mild	Repeated	EPM	No effect of TBI
	Pandey et al., 2009	Rat	Not classified	Single	EPM, hyperemotionality score	Increased emotionality in TBI rats, normalised by escitalopram
	Fromm, 2004	Rat	Not classified	Single	OFT	Increased anxiety in TBI rats, reduced with MgSO4
CCI	Broussard et al., 2018	Mouse	Mild	Repeated	EPM, OFT	Increased anxiety in TBI mice
	Yang, 2015	Mouse	Mild	Repeated	EPM	Increased anxiety in TBI mice
	Petraglia et al., 2014	Mouse (conscious)	Mild	Repeated	EPM	Increased anxiety short term, Increased risk taking long term, in repeated TBI mice
	Washington et al., 2012	Mouse	Variable	Single	OFT, EPM	No phenotype (OFT), or reduced anxiety (EPM) in TBI mice
	Tucker et al., 2017	Mouse	Variable	Single	LDB	TBI mice show reduced (LDB) or Increased (OFT) anxiety
	Watanabe et al., 2013	Mouse	Not classified	Single	EPM, OFT	No phenotype in TBI mice
	Cope, 2012	Rat	Not classified	Single	LDB	Increased anxiety in TBI rats
	Amorós-Aguilar, 2015	Rat	Not classified	Single	EPM	No effect of TBI
FPI	Shultz et al., 2012a	Rat	Mild	Single	OFT, EPM	No effect of TBI
	Shultz et al., 2012b	Rat	Mild	Repeated	EPM	Increased anxiety in repeated TBI mice
	Webster et al., 2015	Rat	Mild	Repeated	EPM, OFT	No effect of TBI
	Shultz et al., 2015	Rat	Moderate	Single	EPM	Increased anxiety in TBI rats, prevented with sodium selenate treatment
	Rowe, 2016	Rat (varying ages)	Moderate	Single	OFT	Increased anxiety in TBI mice
Blast injury	Xie, 2013	Mouse	Mild	Repeated	EZM	Increased anxiety in TBI mice
	Elder, 2012	Rat	Mild	Repeated	EZM, LDB	Increased anxiety in TBI mice
	Perez-Garcia, 2018	Rat	Mild	Repeated	LDB	Increased anxiety in TBI rats, reversed by BCI-818
	Sweis, 2016	Rat	Not classified	Single	Beam walk, EPM	Increased anxiety in TBI rats

Within a given study, consistent phenotypes are usually identified regardless of anxiety test used, although this is not always the case. For example, using the mouse CCI model of varying severity, different tests resulted in different phenotypes: anxiety-like behavior was increased in the Open Field test, but reduced in the Light-Dark Box (Tucker et al., 2017). While it is difficult to explain these differences, this study does highlight the advantage of using more than one tool to assess emotional behavior. In particular, the Open Field has been criticized because it can be difficult to separate general effects on locomotor activity from true anxiety (File, 2001), a potential confound which could have clouded the conclusions of this excellent paper.

Table 3
Summary of studies examining cognition in rodent models of TBI. This field has been studied extensively, so by necessity our table omits several published works from 2014 and for published work prior, readers are directed to detailed reviews (Paterno et al., 2017; Tucker et al., 2018). MWM- Morris water maze, RAM- Radial 8-arm maze.

Model	Citation	Species	Severity	Frequency	Test	Cognitive behaviour changes
Weight drop	(Mychasiuk et al., 2014)	rat	mild	single	MWM, Novel context mismatch	Reduced cognitive function in TBI
	Mychasiuk et al., 2015b	rat	mild	single	Novel context mismatch	Short term memory reduced in both male and female
	(Hou et al., 2017)	rat	Mild/moderate	single	MWM	Acute and chronic cognitive decline in TBI
Closed skull	(Broussard et al., 2018)	mice	mild	Single/repeated	MWM	Acute cognitive decline in repeated TBI
	(Wright et al., 2017a)	rat	mild	Single/repeated	Novel context mismatch	Impairment in working memory in both single and repeated injury
	(Bajwa et al., 2016)	mice	mild	Single/repeated	MWM	Decline in spatial learning in acute and chronic stages in TBI
Blast injury	(Perez-Polo et al., 2015)	rat	mild	single	MWM	Decline in reference memory 5days post TBI
CCI	(Semple et al., 2017a)	mice	severe	single	Y maze	Reduced spatial recognition in male TBI
	(Semple et al., 2017b)	mice	Moderate/severe	Single	MWM	Reduced cognition in TBI
	(Bajwa et al., 2016)	mice	moderate	Single	MWM	Severe cognitive decline
	(Sebastian et al., 2013b)	rat	Moderate	single	RAM	Reduced short term working memory in TBI, no change in long term reference memory
	(Song et al., 2016b)	mice	mild	single	RAM	Reduced working memory in TBI
FPI	(Shultz et al., 2015)	rat	severe	single	MWM	Reduced cognition 12weeks post TBI
	(Johnstone et al., 2015)	rat	moderate	single	MWM	Cognitive decline in TBI
	(Webster et al., 2015)	rat	mild	repeated	MWM	Chronic reduced cognition in TBI
	(Wright et al., 2016a)	rat	mild	repeated	MWM	Reduced cognition in TBI
	(Shultz et al., 2014)	mice	moderate	Single	Y maze	Reduced spatial recognition in TBI

Table 4

Summary of studies examining social behavior in rodent models of TBI. TBI was delivered to anaesthetised adult animals, unless otherwise stated. SIT – Social Interaction Task, SRT – Social Recognition Task, 3CT – 3 Chamber Test, USV – Ultrasonic vocalisations, CCI – Controlled Cortical Impact, FPI - Fluid Percussion Injury.

Model	Citation	Species	Severity	Frequency	Test	Social behaviour phenotype
Weight drop	Pandey, 2009	Mouse	Moderate	Single	SIT	Reduced social interactions in TBI mice
Closed skull	Klemenhagen, 2013	Mouse	Mild	Repeated	SIT, SRT	Reduced social recognition in TBI mice, exacerbated by stress
	Bajwa et al., 2016	Mouse	Mild	Repeated	SRT, scent marking	No effect of TBI
	Nolan et al., 2018	Mouse	Mild	Repeated	3CT	Reduced social memory in TBI mice
	Yu et al., 2017	Mouse	Mild	Repeated	3CT	Reduced sociability in TBI mice
	Semple et al., 2016	Mouse (adolescent)	Mild	Repeated	3CT	No effect of TBI
	Zhang et al., 2015	Rat	Mild	Single	Social odour recognition	Reduced social recognition in TBI rats
	Greco et al., 2015	Rat	Mild	Repeated	Sociosexual interaction	Reduced sociosexual interest in TBI rats
	Dyck and Ivanco, 2018	Rat (juvenile)	Mild	Single	Social play	No effect of TBI
	Mychasiuk et al., 2014a, 2014b	Rat (adolescent)	Mild	Single	Social play	Altered play behaviour in TBI rats; predominantly in females
CCI	Bajwa et al., 2016	Mouse	Moderate	Single	SRT, scent marking	Reduced social recognition in TBI mice
	Davies et al., 2018	Mouse	Severe	Single	SIT	Reduced social interactions in TBI mice
	Semple et al., 2012	Mouse (juvenile)	Severe	Single	SIT, 3CT	Reduced social interactions in TBI mice
	Semple et al., 2014	Mouse (varying ages)	Severe	Single	SIT, 3CT, USV, scent marking	Reduced sociosexual interest and altered communication after TBI at younger age
	Semple et al., 2015	Mouse (juvenile)	Severe	Single	SIT, 3CT	Reduced social recognition in TBI mice
	Semple et al., 2017a, 2017b	Mouse (juvenile)	Severe	Single	SIT, 3CT	Reduced social interactions in TBI, males > females
FPI	Shultz et al., 2012a, 2012b	Mouse	Mild	Single	SIT, SRT	Reduced social recognition in TBI mice
	Shultz et al., 2011	Rat	Mild	Single	SIT	No effect of TBI
Blast injury	Koliatsos et al., 2011	Rat	Mild	Repeated	SIT	No effect of TBI

2.6. Does PTE coincide with depression- and anxiety-like behaviors in models of TBI?

These models of TBI can also be used to explore the relationships between depression- and anxiety-like behaviors and other comorbidities of TBI, such as PTE. PTE is a consequence of several models of TBI (see other reviews in this edition). However, to our knowledge, no studies have been conducted to investigate whether rodents that experience PTE also exhibit exacerbated signs of depression-like behaviors, despite the clear clinical rationale and the relative simplicity of measuring these behaviors. In addition, only one study has explored the extent of anxiety-like behavior and the incidence of PTE following TBI. Shultz et al used the FPI model in male Wistar rats, and observed PTE in 12 out of 23 rats (52%) six months after injury (Shultz et al., 2013). However, when comparing anxiety-like behavior in the open field, and depression-like behavior in the forced swim test, no differences were observed in epileptic- vs non-epileptic rats. This study would suggest that the occurrence of PTE does not coincide with, or predict, anxiety or depression-like behaviors following TBI, or vice versa, but as this is only one isolated report, it certainly requires replication, and expansion using different models.

2.7. Animal models of epilepsy exhibit depression- and anxiety-like behaviors

While it has not yet been established whether models of PTE exhibit elevated levels of anxiety and depression-like behavior – above and beyond that observed following TBI – other animal models of (non-traumatic) epilepsy do exhibit these disturbances (Jones and O'Brien, 2013). This includes models of genetically determined epilepsy (e.g.: Jones et al., 2008; Sarkisova and van Luijtelaar, 2011), but probably more relevant to PTE are animal models of acquired focal epilepsy. For example, the post-status epilepticus (SE) models exhibit histopathological changes similar to those seen in mesial Temporal Lobe Epilepsy, and the ontogenesis of epilepsy development (following a latent period presumably involving reorganization of neuronal connectivity) is also conceptually similar to PTE (Morimoto et al., 2004). Depression-like behaviors, including behavioral despair and anhedonia have been identified in post-SE mouse and rat models (e.g.: Klein et al., 2015; Mazarati et al., 2008; Mazarati et al., 2010), providing vehicles with

which to explore biological mechanisms of depression in epilepsy. Interestingly, this depressive phenotype appears resistant to traditional antidepressant monotherapy (Pineda et al., 2012). Anxiety-like behaviors have also been identified in the post-SE models (e.g.: Liu et al., 2013). However, assessing anxiety in the SE models is somewhat challenging, because the predominant phenotype observed in these tests is one of hyperlocomotion or exploratory activity, and aggression (Huang et al., 2012). These attributes may not be directly related to anxiety, but they can cloud interpretation – for example, an animal that explores an arena more will also enter into the open arms of an Elevated Plus Maze more frequently, thereby appearing less anxious. It is also possible that reductions in anxiety behavior in animal models of epilepsy are related to neuronal damage to the ventral hippocampus, and consequent misevaluation of threatening circumstances (Detour et al., 2005). Finally, it is important to note that variations in both anxiety- and depressive phenotypes following SE can occur when assessing different strains of rodent (Inostroza et al., 2012), suggesting a genetic contribution to susceptibility.

The observations of anxiety- and depression-like behavior in rodent models of epilepsy supports the concept that there exists a biological component to the development of these disorders related to the epilepsy itself, as opposed to a purely psychosocial cause. Such biological factors may be related to the occurrence of seizures occurring in epilepsy, or may be triggered by the same mechanisms which drive epileptogenesis. Further, they support the concept that such behaviors may be associated with PTE in rodent models, thus providing tools to explore the mechanisms underpinning their development, and test therapeutics.

3. Cognition

3.1. TBI can result in a range of cognitive impairments in patients

Cognitive impairments are amongst the most common and debilitating consequences of TBI. The term "cognition" encompasses a range of mental processes including attention, learning, executive function, and memory, amongst others. It is therefore not surprising that a vast number of previous studies have investigated cognitive outcomes in TBI patients. This section will provide a brief overview of the broad spectrum of cognitive abnormalities that have been reported in TBI patients to aid in interpreting the translational value of the pre-clinical TBI

findings discussed below. For more comprehensive reviews focused on cognitive impairments in TBI patients the reader is directed to previous papers (e.g.: Azouvi et al., 1996; Beauchamp and Anderson, 2013; Cristofori and Levin, 2015; Rabinowitz and Levin, 2014; Vakil, 2005; Wood and Worthington, 2017).

In summary, studies investigating cognitive abnormalities in TBI patients have found evidence for impairments in attention (Fenwick and Anderson, 1999; Ponsford and Kinsella, 1992), speed of information processing (Azouvi et al., 2009; Vallat-Azouvi et al., 2009), mental fatigue (Masson et al., 1996; Ziino and Ponsford, 2005), learning (DeLuca et al., 2000; Demery et al., 2002), executive function (Azouvi et al., 2009; Clough et al., 2018; Wood and Worthington, 2017), problem solving (Cazalis et al., 2006), short-term and working memory (Azouvi et al., 1996; Haut et al., 1990; Levin et al., 1976; Vallat-Azouvi et al., 2007), and long-term memory (i.e., both anterograde and retrograde amnesia; e.g., Azouvi et al., 2009; Carlesimo et al., 1998; Piolino et al., 2007; Zec et al., 2001). The clinical presentation of these deficits after TBI can be immediate or delayed, and they can be transient, evolving, or permanent in nature (Azouvi et al., 2009; Belanger and Vanderploeg, 2005; Manley et al., 2017; McMahon et al., 2014; Vakil, 2005). The heterogeneity of cognitive impairments post-TBI is dependent on a number of different factors that can include TBI severity, the injury mechanism, brain regions affected, age, pre-existing cognitive capacity, and genetics (Azouvi et al., 2009; Beauchamp and Anderson, 2013; Cristofori and Levin, 2015; Davidson et al., 2015; Demery et al., 2002; Manley et al., 2017; Rabinowitz and Levin, 2014; Vakil, 2005). As already alluded to, and discussed further below in the context of cognition, the development of PTE is another factor that could influence behavioral co-morbidities in TBI patients.

The large degree of variability in cognitive outcomes and possible modifying factors (e.g., epilepsy) in the clinical TBI setting, along with other challenges related to clinical TBI research, makes it difficult to succinctly characterize the sequelae of cognitive impairments after TBI and determine underlying mechanisms in individual patients. Animal model studies provide a means to investigate cognition after TBI in a highly controlled manner (Shultz et al., 2017). As described below, previous studies utilizing animal models of TBI have found a spectrum of cognitive abnormalities at acute, sub-acute, and chronic stages post-injury, many of which bear similarities to those observed clinically.

3.2. TBI can result in a range of cognitive abnormalities in rodents

Cognitive deficits are frequently detected in experimental models of TBI, with spatial learning and memory deficits being the most commonly studied in rodents (Table 3). The Morris water maze (MWM), which involves training of rodents to use visual spatial cues to locate a hidden escape platform in a pool of water, was developed in the early 1980s and has been extensively used to study spatial learning and memory deficits (Morris, 1984). The Barnes maze, first described in 1979 (Barnes, 1979), is another common task to evaluate spatial learning and memory in rodents. It has the advantage that it eliminates the stress associated with water/swimming based tasks and instead relies on a mildly aversive stimulus such as a light as motivation for rodents to locate an escape hole (Fox et al., 1998; Rosenfeld and Ferguson, 2014). The radial 8-arm maze (RAM) uses food-based rewards to assess working and retrieval memory, as well as spatial learning in rodents, with performance linked to hippocampus and prefrontal cortex function (Olton and Samuelson, 1976; Soblosky et al., 1996).

The MWM and the Barnes maze have been commonly used in previous preclinical TBI studies to identify cognitive deficits. Indeed, the use of the MWM in translational TBI research is the topic of review papers in and of itself (see Tucker et al. (2018) for recent review). For example, MWM studies have found evidence for abnormalities in learning, cognitive flexibility, and working memory, as well as retrograde and anterograde amnesia in rodents given a TBI (Bao et al., 2012;

Hamm et al., 1992; Hamm et al., 1996; Hoane et al., 2004; Johnstone et al., 2015; Lindner et al., 1998; Peterson et al., 2012; Smith et al., 1991; Smith et al., 1995; Tan et al., 2016; Thompson et al., 2006; Washington et al., 2012; Wright et al., 2016b). Similarly, spatial learning and memory deficits in the Barnes maze have been found to be present at various post-injury times in rodent models of TBI (Fedor et al., 2010; Fox et al., 1998; Paterno et al., 2017; Vink et al., 2003). The brain region most commonly implicated in spatial learning and memory deficits in these tasks is the hippocampus (Buzsaki and Moser, 2013; Okeefe and Nadel, 1979), though a number of other structures (e.g., entorhinal cortex, frontal cortex, parietal cortex, corpus callosum) and pathophysiological mechanisms (e.g., hyperphosphorylated tau, inflammation, oxidative stress) have been implicated as well (Bao et al., 2012; Buzsaki and Moser, 2013; Johnstone et al., 2015; Shultz et al., 2015; Tan et al., 2016; Webster et al., 2015; Wright et al., 2016b). Of note, virtual water maze tasks have been adapted to test spatial learning and memory in humans, and TBI patients display deficits on this task (Skelton et al., 2006), highlighting the translational potential of the above preclinical TBI findings.

TBI has shown to affect both short and long-term memory in this task (Enomoto et al., 2005; Lyeth et al., 1990). For example, the Radial 8-arm maze (RAM) test was able to discriminate between an intact reference memory and deficits in spatial working memory in rats at two weeks after CCI. Longer recovery in conjunction with robust training in these animals proved to be effective in reducing working memory errors (Sebastian et al., 2013a). Exposure to the RAM prior to experimental TBI can also protect against post-injury cognitive deficits (Kreipke et al., 2007). In addition, certain treatments such as hematopoietic growth factor injections (Song et al., 2016a), inhibition of a pro-inflammatory mediator (Corser-Jensen et al., 2014) or activities such as treadmill exercise (Shin et al., 2016; Taylor et al., 2015) have been shown to enhance performance in the RAM task following TBI.

The Y-maze and T-maze are other tests used to assess spatial learning, as well as reference and working memory, in rodents. First described by Dellu and colleagues (Dellu et al., 1992), the Y maze involves a familiarization/habituation phase whereby rodents can freely explore two of the maze arms, followed by a test phase when they are exposed to the previously-closed novel arm. The amount of time spent in the novel arm is an indication of their working memory and exploration tendency (Yau et al., 2007). In contrast, the T-maze involves providing rodents with a choice to go left or right at the intersection of the T, and depending on the protocol, testing can involve assessing either spontaneous left-right discrimination/alteration, or either the left or right can be baited with a reward (Sharma et al., 2010). Injury to the brain reduces time spent in the novel arm compared to sham animals, interpreted as a deficit in spatial working memory (Shultz et al., 2014; Tchantchou and Zhang, 2013). Further, mice given a TBI have been found to have both acute and persistent working memory deficits in the T-maze (Hoskison et al., 2009; Smith et al., 2015). Memory deficits after TBI in the T-maze and Y-maze have been linked to a number of neuroanatomical structures including the hippocampus, prefrontal cortex and hippocampus (Shultz et al., 2014; Smith et al., 2015).

The Novel Object Recognition (NOR) test, initially described in 1988 (Ennaceur and Delacour, 1988), evaluates recognition memory by exposing rodents to two identical objects during a familiarization/habituation phase, followed by replacement of one of these objects with a novel object, usually after a pre-determined time interval. Healthy animals recognize the novel object using hippocampal-dependent recognition memory (Bevins and Besheer, 2006). This test has revealed short and long-term cognitive deficits in rat and mouse TBI models (Fidan et al., 2016; Iliff et al., 2014; Prins et al., 2010; Wakade et al., 2010). These impairments may be due to hippocampal injury, axonal damage and/or tau aggregation (Iliff et al., 2014; Ohta et al., 2013; Wakade et al., 2010). Importantly, these findings are consistent with preliminary clinical studies indicating that TBI patients also have impairments in recognition memory (Millis and Dijkers, 1993). An

extension of the NOR, the Novel Context Mismatch (NCM) test is used for assess novel object recognition, as well as context (i.e. the ability to associate objects with an environment) and spatial memory (Dix and Aggleton, 1999; Mumby et al., 2002). This test is sensitive enough to detect cognitive deficits even in models of single and repetitive mild TBI (Mychasiuk et al., 2016; Wright et al., 2017b).

Finally, the 5-choice serial reaction time task (5-CSRTT) (Bari et al., 2008; Robbins, 2002) assesses attention versus impulse behavior. It is based on the principles of the human continuous performance task (Robbins, 2002), and is most commonly used in the context of attention deficit hyperactivity disorder. Attention is an important component of cognition, and attention deficits are common in TBI patients (Fenwick and Anderson, 1999; Ponsford and Kinsella, 1992). Indeed, TBI patients consistently display deficits on the continuous performance task (Riccio et al., 2002), which illustrates the translational value of the 5-CSRTT. Deficits in this task have been detected after mild TBI in young rats, indicating problems with attention and impulsivity behavior (Mychasiuk et al., 2015a). Another study investigated the effects of mild, moderate, and severe frontal TBI on 5-CSRTT performance in mature rats, and found that mild TBI induced persistent impulse control abnormalities, while moderate and severe injured rats had persistent deficits in attention, impulse control, and motivation (Vonder Haar et al., 2016).

3.3. Does PTE worsen cognitive deficits after TBI?

As evidenced in the above-mentioned studies, TBI can induce cognitive impairments in humans and rodents. In addition to these cognitive deficits, it is not uncommon for TBI patients to develop PTE. Epilepsy in and of itself is strongly associated with a range of cognitive co-morbidities. In epilepsy patients, this includes deficits in attention, learning, short- and long-term memory, and executive function (Griffith et al., 2007; Martin et al., 2005; Miller et al., 2016; Sen et al., 2018; Witt and Helmstaedter, 2015; Witt et al., 2014). Further, the effects of epilepsy on cognition in rodent models is also well documented. Deficits in learning and spatial recognition has been reported in kainic acid- (Letty et al., 1995; Lynch et al., 2000; Muller et al., 2009) and pilocarpine-induced chronic epilepsy models (Harrigan et al., 1991; Hort et al., 1999; Mohajeri et al., 2003; Sroubek et al., 2001). Attention deficits in the 5-CSRTT has also been found in the pilocarpine-induced epilepsy rat model (Faure et al., 2014). RAM abnormalities have been found in the kainic acid, pilocarpine, and hippocampal kindling models of epilepsy (Cook et al., 1985; Kotloski et al., 2002; Leite et al., 1990; Leung and Shen, 2006; Sarkisian et al., 1997; Sayin et al., 2004; Sutula et al., 1995; Wu et al., 2001). Furthermore, the diisopropylfluorophosphate-induced SE model in rats results in NOR deficits (Rojas et al., 2016), and pilocarpine-induced seizures induce novelty recognition dysfunction in mice (Cho et al., 2015).

Considering that both TBI and epilepsy are associated with cognitive deficits, it stands to reason that TBI patients who later develop PTE (i.e., a double hit) may eventually have worse cognitive deficits than their counterparts who do not develop PTE (Breuer et al., 2016; Sen et al., 2018). However, only a handful of studies have attempted to investigate this question to date. In a cohort of 143 severe TBI patients, the subset of 27 who developed PTE had worse inhibitory deficits and functional outcomes at one year after TBI, but there were no differences on measures of memory, intelligence, attention, and spatial cognition between the TBI patients with or without epilepsy (Mazzini et al., 2003). A study by Haltiner et al. (1996) found that TBI patients who had one or more late posttraumatic seizures had more severe deficits on a range of cognitive measures one year after injury when compared to TBI patients who did not experience late seizures. However, when the severity of the TBI was controlled for there were no differences between the different TBI groups. This led the authors to conclude that the more severe impairments in the TBI + late seizure patients were attributed to TBI severity (i.e., more severe in the TBI + seizure patients) and not the

seizures (Haltiner et al., 1996). On the other hand, another study that investigated TBI outcomes in groups of patients with or without late posttraumatic seizures that were matched on demographic and injury characteristics found that TBI patients with late posttraumatic seizures had worse functional independence measure (FIM) cognitive subscale scores at 1, 3, and 5 years after TBI (Bushnik et al., 2012). Another study in combat TBI patients, most of which involved a penetrating TBI, investigated intelligence using the Armed Forces Qualification Test for up to 35 years post-injury (Raymont et al., 2010). It was found that PTE was predictive of current intelligence and intelligence decline even when controlling for pre-injury intelligence and brain volume loss.

Similar to these clinical studies, preclinical findings on this topic have also been mixed. In a study that looking at TBI rats comparing those that did or did not develop PTE, Shultz and colleagues found no significant differences in MWM performance between the groups at six months post-injury (Shultz et al., 2013). Meanwhile, other preclinical TBI studies do provide some evidence that cognitive deficits may be worsened by PTE. For example, mice that were given a TBI followed by seizures induced by electroconvulsive shock had worse impairments on the Barnes maze compared to mice that were only given a TBI (Chrzaszcz et al., 2010). Furthermore, these findings were associated with increased glial activation in the "double hit" mice. Taken together, the few studies that have examined the effects of PTE on cognitive outcomes have provided inconclusive results. Temporal complexities may account for the failure of some of the studies to identify differences between TBI versus TBI + PTE groups. Specifically, these studies may have been limited by the relatively short post-PTE recovery times examined. The development of PTE can take months to years post-injury, and therefore the additional cognitive burden of the PTE may not have had sufficient time to manifest in these studies. Whether or not PTE worsens cognitive function after TBI remains to be determined and should be a priority for future studies, particularly considering how common and detrimental cognitive deficits are in TBI and epilepsy.

4. Social behavior

4.1. Social behavior deficits are common after TBI and epilepsy

Social dysfunction is one of the most debilitating and persistent problems reported after TBI, in both adults and children (Dikmen et al., 1995; Hoofien et al., 2001; Rosema et al., 2012). A large body of clinical literature demonstrates that TBI survivors are at increased risk of reduced social interactions, social cognition, verbal and non-verbal communication, and adaptive behavior, as well as an increased risk of heightened aggression and anti-social behaviors (Rosema et al., 2012; Ryan et al., 2016; Yeates et al., 2004). In contrast to motor and physical symptoms, which typically stabilize or resolve over time, psychosocial impairments are reported to cause the greatest long-term distress for patients and their families (Catroppa et al., 2012; Chapman et al., 2010). Social deficits have been documented in the acute, sub-acute and chronic phases after TBI, particularly associated with focal contusions, although reported across a range of injury severities (Ryan et al., 2016). Social deficits are a particular problem after TBI during early childhood, whereby a head injury during the usual maturation of social behaviors appears to adversely affect the acquisition of new social skills (Wells et al., 2009). Problems with social cognition, or social information processing, as well as social communication, have been reported to persist up to 20 years after severe childhood TBI (Hoofien et al., 2001; Ryan et al., 2016). The consequences of such social behavior problems are not trivial. Indeed, it is increasing recognized that social functioning is a key contributor to long-term quality of life (QoL), by affecting an individual's ability to participate in school or employment, live independently, and form or maintain meaningful relationships (Rosema et al., 2012).

Similarly, a significant proportion of patients with epilepsy experience difficulties with social functioning (Caplan et al., 2008; Szemere

and Jokeit, 2015). Reduced participation in social activities is associated with increased seizure frequency, particularly in patients with intractable or medically-refractory epilepsy (Leidy et al., 1999; Strine et al., 2005), as seizures appear to have a profound impact on an individual's ability to participate fully in the community. However, other studies have also reported that social functioning is compromised even amongst individuals with childhood and juvenile onset generalized epilepsies who are currently seizure-free, so regardless of seizure control (Camfield and Camfield, 2014; Engelberts et al., 2002; Nickels, 2015). In a recent cohort study of 159 children with epilepsy, approximately half exhibited emotional and behavior problems, with social and attention deficits being more common than externalizing behaviors (Dal Canto et al., 2018). In general, problems with language and social communication, social competency, relationships, and social cognition are reported at a higher incidence in children with epilepsy compared to normal controls, with seizure frequency, duration of the condition, as well as anti-epileptic medication being influencing factors (Caplan et al., 2008). By adulthood, individuals who had epilepsy during childhood exhibit particularly high rates of social problems, even if they are neurologically and intellectually within a normal range (Camfield and Camfield, 2014). Adults with a range of epilepsies, both focal and generalized, acquired and genetic in origin, report persistent challenges with social engagement and interpersonal relationships, which likely contributes to their reduced rates of marriage and employment (Broicher et al., 2012; Jalava and Sillanpaa, 1997; Strine et al., 2005).

4.2. Social dysfunction in experimental models of TBI and epilepsy

Changes in social behavior as a consequence of TBI, seizures or epilepsy, have also be detected in experimental animal models, primarily in rodents (Table 4). Rats and mice display a broad repertoire of social behaviors that can be objectively quantified, typically by the observation of social approach and investigation of conspecifics. The most common paradigm for social interactions involves allowing the test subject free exploration for a limited period of time with an unfamiliar animal. The 'stimulus' animal may be matched to the test subject for sex, age and strain (Koolhaas et al., 2013), or alternatively be of a juvenile age to minimize potential aggressive behaviors being exhibited (Kaidanovich-Beilin et al., 2011; Terranova and Laviola, 2005).

A more refined task involves physical separation of the test subject and the stimulus animal, with the stimulus animal restrained in a small enclosure within the test arena, to restrict the initiation and motivation of social approach to the test subject specifically, and limit interactions to the visual, olfactory and auditory senses (Moy et al., 2008; Nadler et al., 2004; Silverman et al., 2010). This three-chamber social approach task, originally developed to characterize autism-like phenotypes in mouse models, remains the gold-standard test to evaluate sociability in rodents. Three consecutive stages of this task test an animal's preference for sociability and then social recognition/social memory (Moy et al., 2008; Silverman et al., 2010).

In addition, several tests for social communication have been established in rodents, and changes in these measures have emerged as a signature characteristic of autism-like mouse models alongside a reduction in social interactions (Wöhr and Scattoni, 2013). These tasks involve detecting changes in urinary scent marking (Arakawa et al., 2008) and emitted vocalizations in the ultrasonic range during social interactions (Wöhr et al., 2011), and are considered to be indicators of social dysfunction in rodents. Finally, using a stimulus animal of the opposite sex to the test subject allows for the evaluation of socio-sexual interactions specifically (Arakawa et al., 2007).

Using these tests, social behavior changes have been detected in a range of experimental TBI models, including CCI (Chou et al., 2016; Semple et al., 2012; Semple et al., 2017b; Semple et al., 2014), FPI (Fenn et al., 2013), impact acceleration (Pandey et al., 2009), blast

(Koliatsos et al., 2011) and repetitive closed skull impacts (Klemenhagen et al., 2013; Yu et al., 2017). In general, a reduction in social investigation, social recognition memory, and social communication has been reported after TBI in both adult and juvenile rodents. Social behavior deficits appear to depend upon younger age at the time of injury (Semple et al., 2014), longer time post-injury (Semple et al., 2012), injury severity (Davies et al., 2018; Shultz et al., 2012a; Shultz et al., 2011), and injury location (Chen et al., 2013; Chou et al., 2016). After TBI in three-week old mice, reduced social and socio-sexual interactions as well as changes in social communication are delayed in appearance, emerging by adulthood, consistent with clinical literature indicating that social problems develop over time after TBI in young patients (Ryan et al., 2016).

Social behavior deficits have also been reported in experimental models of acquired and genetic epilepsies. Selective breeding strategies have generated rat strains with differing susceptibility to developing epilepsy, and their study have provided valuable insight into the biological basis of susceptibility to developing acquired epilepsy (Racine et al., 1999). These models have demonstrated that behavioral comorbidities are associated with increased susceptibility to acquired epilepsy, including social behavior impairments (Henbid et al., 2017; McIntyre and Gilby, 2007). Similarly, models of acquired epilepsy, such as the pilocarpine model, result in reduced social interactions compared to age-matched saline-injected controls (Minjarez et al., 2017). Kainic acid administration to induce acquired epileptogenesis in rats results in a significant deficit in social recognition memory, which was not the case for amygdala-kindled epileptic rats (Letty et al., 1995). As the former model results in considerable neuronal loss, compared to only minor structural lesions in kindled animals, the authors of this comparative study infer that social deficits in epilepsy are thus dependent upon the extent of neuropathology associated with the condition, rather than the development of seizures *per se.*

4.3. Does PTE worsen social behavior deficits after TBI?

With evidence that both TBI and epilepsy separately contribute to social behavior problems to negatively impact QoL, the question arises about whether epilepsy as a consequence of TBI, i.e. PTE, acts as a second-hit insult to worsen social outcomes in TBI patients. Determining the effect of seizures on psychosocial functioning in TBI patients is important to clarify, as it informs the degree of benefit to be gained by seizure prevention strategies, and whether these is sufficient to justify exposing patients to the potential side effects of anti-epileptic medications (Haltiner et al., 1996).

Individuals with TBI and late post-traumatic seizures (LPTS), defined as more than one seizure greater than one week post-injury, are often thought to be at a 'double-barreled disadvantage' regarding ongoing psychosocial issues (Kolakowsky-Hayner et al., 2013). Few studies, however, have directly compared TBI patients with versus without PTE, to objectively evaluate this premise (Bushnik et al., 2004). One study examining the association between outcomes with early and late seizures after TBI, in a cohort of 490 patients up to 5 years post-injury, found that LPTS correlated with poorer functional outcomes, whereby those with late seizures more often had a Glasgow Outcome Score (GOS) of 2 or 3 (= severe disability or persistent vegetative state) compared to those who did not have seizures (Asikainen et al., 1999). Similarly, Grafman et al. (1992) found that post-traumatic seizures in Vietnam War veterans with combat-related penetrating head injuries were associated with poorer performance on a range of neuropsychological tests administered 15 years after injury, even after controlling for the volume of brain tissue loss quantified by CT imaging at this time (Grafman et al., 1992).

In contrast, Haltiner et al. (1996) examined 210 individuals with moderate to severe TBI +/− PTE prospectively followed for 1 year post-injury. As expected, TBI patients with LPTS were those who sustained the most severe head injuries, and had more pronounced

psychosocial function impairments compared to those without LPTS. However, after ensuring that the groups were matched for acute injury severity, psychosocial outcomes (defined from the GOS, employment status and living arrangements) were no different between TBI survivors with PTE compared to those who remained seizure-free (Haltiner et al., 1996).

Finally, most recently, a prospective survey of 182 individuals with TBI at 1, 2 and 5 years post-injury, reported that those with LPTS had higher Disability Rating Scale scores up to 5 years, indicating greater functional disability than those without LPTS, despite both groups having similar scores at discharge from rehabilitation. Those with LPTS also showed consistently lower Satisfaction With Life Scale scores, a global measure of life satisfaction (Bushnik et al., 2012). Collectively, these studies suggest that, at a population level, LPTS do confer a degree of additional psychosocial impairment to those with TBI. Of note, however, individual differences in seizure severity and frequency, and the period of time over which seizures have occurred, may also be factors that influence whether adverse psychosocial consequences develop.

While preclinical studies have demonstrated that experimental TBI results clinically-relevant behavioral comorbidities, including psychosocial deficits, alongside PTE in a subset of animals (Pitkanen et al., 2014), a causal relationship between LPTS and social impairments in TBI animals has not yet been explored. Most studies to date have examined one outcome or the other, without any correlative analysis, such that the temporal relationship between behavioral deficits and the development of epilepsy after TBI has not yet been characterized. This is somewhat surprising, as many models such as FPI and CCI result in spontaneous epileptic seizures in a proportion of animals (typically 30-50%), allowing for within-study comparison of behavioral outcomes in TBI animals that develop epilepsy versus those that do not.

4.4. Potential neurobiological mechanisms linking TBI, PTE and behavioral dysfunction

Several neurobiological candidates exist which could lead to behavioral disorders following TBI, and these could be worsened by PTE. It is likely that one specific mechanism is not exclusively responsible, but a network of changes at several different levels – molecular, cellular, circuit – could together result in the different behavioral outcomes discussed above. Several of these candidates are discussed at length in other chapters of this Special Edition, especially those by Ali et al. (2018)) and Saletti et al. (2018). We encourage readers to examine those articles for in-depth commentary regarding the evidence supporting such mechanisms. We will briefly discuss three possible contributors, but stress there are certainly others worthy of attention.

Inflammatory processes are intimately involved in the pathogenesis of both TBI (Webster et al., 2017) and acquired epilepsy (Maroso et al., 2010), and therefore may be key factors in the development of posttraumatic epilepsy. Behavioral deficits, in particular affective disorders (Raison et al., 2006), are also closely associated with elevations in proinflammatory cytokines and other neuroinflammatory events, and so this appeals as a strong neurobiological candidate explaining behavioral comorbidities in PTE, also an attractive prospect since anti-inflammatory treatment options are available. Neurogenesis is also heavily implicated in these pathologies, with TBI and seizures acutely resulting in bursts of new-born neurons within the dentate gyrus of the hippocampus (Dash et al., 2001; Parent et al., 1997; Kumar et al., 2011). This brain structure is intimately involved in memory and other cognitive processes, as well as affective disorders, so abnormal neurogenic processes in this area may influence these behaviors. However, neurogenesis is *negatively* regulated by stress (Gould and Tanapat, 1999), and chronic stress is commonly associated with depressive disorders as well as epilepsy. This dichotomy of neurogenesis regulation – upregulated by TBI and seizures, but downregulated in affective conditions – would argue against this mechanism being responsible for behavioral comorbidities in PTE. However, several studies show that, following seizures, although there are more neurons born, these aberrantly migrate to the dentate hilus, which alters the properties of this brain region and could therefore lead to behavioral and cognitive disorders (Cho et al., 2015). Alternatively, it appears that in the chronic disease state of epilepsy, neurogenesis rates are markedly slowed (Hattiangady et al., 2004) – a property which could also induce susceptibility to affective conditions and possibly also impaired cognition. A third possibility involves neurodegenerative pathways triggered by TBI and exacerbated by PTE. Incorporating general brain atrophy as well as tau pathology, inflammation, and other cascades, these are strongly linked to cognitive disturbances and also depressive disorders, and so may also act as mechanisms resulting in behavioral comorbidities of PTE (G.Saletti. et al., In press).

5. Conclusions and future directions

Although abundant evidence now demonstrates that patients with either TBI or epilepsy are at increased risk of impairments in cognitive, social and emotional functioning, the biological mechanisms that underlie these behavioral changes remain incompletely understood. In the context of TBI, it is hypothesized that injury affects the temporo-limbic circuitry involved in normal emotional social information processing and psychosocial function (Ryan et al., 2016). As such, impairments in social and emotional function can arise from traumatic lesions throughout the nodes or pathways of this network (Bigler et al., 2013; Ryan et al., 2013). Temporal and frontal lobe epilepsies have similarly been associated with neuropathology within these brain circuits (Broicher et al., 2012).

The pathological mechanisms of secondary injury triggered by a TBI, such as excitotoxicity, neuroinflammation, oxidative stress, axonal injury, blood-brain barrier disruption, and excitatory/inhibitory dysfunction, have also been implicated in epileptogenesis, the process by which a normal brain becomes epileptic (Webster et al., 2017). Many of these same biological processes that precipitate seizure occurrence in epilepsy may also contribute to the development of chronic neurological and behavioral deficits, depending on the brain region most affected as well as a number of other factors. Further, the relationship between seizure disorders and behavioral dysfunction is unlikely to be a simple one, with increasing evidence of a bidirectional interplay between seizures and psychiatric symptoms, in particular (Kanner et al., 2014). Indeed, premorbid depression is an identified risk factor for the development of PTE (Ferguson et al., 2010). To better understand the biological, mechanistic relationship between neurotrauma, epilepsy and behavior, it is imperative that both seizures and neurobehavioral outcomes are assessed in parallel, both in patient populations and preclinical models. Therapeutics to both prevent the development of PTE as well as the behavioral comorbidities can then be tested appropriately. The other aspect to consider from a treatment perspective is that the same neurobiological consequences of TBI that lead to epilepsy may be the very same as those that lead to behavioral disorders, thereby having common causal elements (regardless of their interactions). As such, development of disease-modifying therapies may be beneficial in treating or preventing the occurrence of these comorbidities.

Importantly, clarifying the impact of PTE on cognitive, affective and social functioning in TBI patients is necessary to gauge the potential benefit to be gained by seizure prevention strategies, and balance this benefit against the treatment side effects. It should be noted that the use of anti-epileptic drugs, which may also affect cognition and psychosocial function, is a common confounding variable in many patient studies (Sen et al., 2018). Many anti-seizure medications are known to negatively impact functional outcomes, with side-effects including sedation and attention deficits as well as cognitive impairments. Indeed, for each additional drug, an additional reduction in executive function is reportedly observed (Witt et al., 2015) This is a particular concern for TBI patients with PTE, with a large proportion being on a combination

of several anti-seizure treatments (i.e. polytherapy) and/or exhibiting drug-resistant epilepsy (Larkin et al., 2016; Raymont et al., 2010). Thus behavioral comorbidities associated with epilepsy and PTE may not solely be attributed to seizure activity *per se*. Dissecting the relative contributions of seizures, TBI, pre-existing psychiatric conditions, and medications to behavioral comorbidities in this population remains an unmet challenge.

Although described above as distinct behavioral domains, there is considerable overlap in terms of the presentation of deficits in the same patient, and the likely underlying mechanisms. As mentioned earlier, psychiatric and affective co-morbidities are common in this population, as are deficits in cognitive processing such as memory and attention, which may hinder the processing of social and emotional information (Steiger and Jokeit, 2017). Cognitive deficits can also impact verbal and non-verbal communication, thus impairing social interactions and social cognition. In addition, psychological considerations such as the effect of social stigma, societal expectations, the effect of parental overprotectiveness and fear of seizure occurrence should not be underestimated (Jacoby et al., 2009; Szemere and Jokeit, 2015). Complicating matters further, in individuals with PTE, TBI alone may also result in psychological and cognitive impairments which influence social functioning. Finally, socioeconomic factors such as social support networks, access to health care, education and cultural environment can all influence an individuals' level of functioning across behavioral domains, and hence affect quality of life (Ryan et al., 2016; Steiger and Jokeit, 2017).

In summary, abundant evidence from clinical and preclinical studies demonstrates that TBI and epilepsy both manifest with behavioral co-morbidities that can have a profound impact on an individual's QoL. Although discussed above independently, there is considerable overlap between psychiatric, cognitive and social behavior domains, with symptoms commonly presenting concurrently across a spectrum. While it stands to reason that the superimposition of epilepsy on TBI (i.e. PTE) would yield an additive detrimental burden, surprisingly few studies have explored both seizures and behavior in the same subjects, nor investigated the likely overlapping biological mechanisms that underlie these comorbidities. Based on the published literature, conflicting reports that suggest that PTE can be either associated with worse functional outcomes (Asikainen et al., 1999; Bushnik et al., 2012; Chrzaszcz et al., 2010; Grafman et al., 1992), or has no effect compared to those with TBI alone (Haltiner et al., 1996; Mazzini et al., 2003; Shultz et al., 2013). Further well-controlled studies, both in patient populations and experimental models, are clearly warranted to establish conclusive evidence.

Conflicts of interest

None.

Acknowledgements

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