

# **PSYCHOLOGICAL TREATMENTS FOR DEPRESSION FOLLOWING BRAIN INJURY**

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### **STATEMENT OF ORIGINALITY**

This is to certify that to the best of my knowledge the content of this thesis is my own work.

This thesis has not been submitted for any degree or other purposes.

I certify that the intellectual content of this thesis is the product of my own work and that all the assistance received in preparing this thesis and sources have been acknowledged.

Signed:

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Dated: 13 December 2019

## AUTHORSHIP ATTRIBUTION STATEMENT

Chapter 2, section 1 of this thesis is published as Gertler, Tate, and Cameron (2015).

*I developed the concepts of the review, created the protocol with the assistance of the co-authors, undertook and coordinated all aspects of the systematic review and authored the final publication.*

Chapter 3 of this thesis is published as Gertler and Cameron (2018).

*I conceptualised the scope of the paper, conducted an extensive literature search and wrote the drafts of the manuscript.*

Chapter 4 of this thesis is published as Gertler and Tate (2020).

*I designed the study and coordinated all aspects of it including seeking ethical approval, organising data collection and undertaking the majority of data collection personally. I collated data, analysed the results and wrote the drafts of the manuscripts.*

Chapter 5 of this thesis is published as Gertler and Tate (2019).

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## LIST OF PUBLICATIONS AND PRESENTATIONS

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## Presentations

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## ABSTRACT

Traumatic brain injury (TBI) increases risk of depression which is distressing and can be a barrier to recovery. This program of research examined non-pharmacological interventions for people with depression following TBI. A Cochrane systematic review was conducted in order to identify studies of interventions (Gertler, Tate, & Cameron, 2015; Chapter 2, section 1). Cochrane reviews are the most stringent form of systematic review of evidence relating to treatment outcomes. The review identified six studies, three studies relating to cognitive-behavioural therapy (CBT) which were combined in a meta-analysis that showed a very small effect in favour of treatment versus control, with a wide confidence interval. Other treatment studies were evaluated but either did not favour any treatment or were low quality studies. Recent studies have reported positive findings for CBT extended by booster sessions or for acceptance and commitment therapy (Chapter 2, section 2). Chapter 3 (Gertler & Cameron, 2018) is a published journal article explaining data analytic techniques used in a Cochrane review. Chapter 4 describes a psychometric evaluation of single-item mood scales (SIMS; Gertler & Tate, 2020) that can be used to demonstrate progress in treatment. SIMS are frequently used in clinical practice but had not yet been shown to be valid when used with people with brain impairment. SIMS were demonstrated to have construct and criterion validity when applied to TBI. Chapter 5 (Gertler and Tate, 2019) is a published journal article describing a single case experimental design (SCED) trial of behavioural activation (BA) to improve participation and mood. BA was chosen because it had not been evaluated for people with TBI and was thought to be more suitable than treatments such as CBT that require abstract thinking. The authors did not find evidence in favour of BA and this was discussed in the context of recent research findings that

suggested that new technologies could improve the quality of measurement and interventions. In conclusion, there is more research to do in order to improve the effectiveness of interventions for depression after TBI however, using SIMS as a measure and SCED methodology, the thesis demonstrates a model for investigating untested interventions and their active components.

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## **CHAPTER 1**

### ***Introduction***

## **1.1 Rationale for thesis**

### *Common clinical questions*

This program of research was prompted by several clinical questions that the author encountered during more than a decade of clinical practice in neurorehabilitation. Clinical psychologists, clinical neuropsychologists, psychiatrists, rehabilitation physicians and other health professionals working in neurorehabilitation frequently encounter people who are suffering from depression following a traumatic brain injury (TBI). The interventions for supporting people with depression have been developed in populations without neurological impairments and therefore the first question that arose was “are existing interventions applicable to people with TBI?” Second, “how effective are these interventions?” and third, “are some interventions more effective than others?” During the course of conducting this research program, another question that arose was “how can we best track mood to see whether treatments are working?” Finally, “is it possible to identify a successful intervention for depression post-TBI that would be applicable to clinical practice?”

## **1. 2 Traumatic Brain Injury**

### 1.2.1 Mechanisms of TBI

In TBI damage to the brain is caused by external forces which can include direct impact, rapid acceleration or deceleration, a penetrating injury, crushing of the skull and blast waves from an explosion. These external forces vary greatly along parameters of intensity, location, direction, and duration and determine the resulting consequences of the injury



(viz. impairments; Maas, Stocchetti, & Bullock, 2008). Common causes of TBI include motor vehicle crashes, workplace accidents (e.g. being hit on the head by falling objects), assaults and falls. Recently there has been renewed interest in TBI caused by sporting injuries often with repeated sub-concussive head knocks (Kontos, Reynolds, & Gillie, 2019). In the context of military conflicts from 2000 to 2017, more than 300,000 US service personnel suffered mild TBI due to blast injuries from improvised explosive devices (Karr et al., 2019).

TBI occurs when the brain is subject to external force that has a neurological consequence (McGarity, Brenner, & Corrigan, 2019). Such consequences include any loss or decrease of consciousness, loss of memory for events before or after the injury, neurological deficits (e.g. weakness or sensory loss), or any alteration in mental state at the time of the injury such as confusion/disorientation (Menon, Schwab, Wright, & Maas, 2010). Clinical presentations after TBI are heterogenous and can affect individuals of any age. TBI may cause temporary and/or permanent changes in cognitive function, emotional regulation, behavioural control, physical abilities. The initial disruption to memory and consciousness is such that there is a period retrograde amnesia (forgetting of information learned prior to the injury), a period of altered consciousness or coma, and then a period of post-traumatic amnesia (PTA) during which the person is unable to lay down new memories, although they might have some recollections of events from this time, so called “islands of memory” (Griffen & Hanks, 2014). These changes may lead to further limitations and restrictions in the person’s ability to fulfil their usual activities within domains of personal care, socialising and interpersonal relationships, occupational and/or leisure pursuits.

Injuries can be focal or diffuse and relate to the mechanical conditions in which the TBI occurs. There is primary damage occurring at the time of the accident and secondary damage which might present after a delay. Meaney, Morrison, and Bass (2014) reviewed the literature and noted that the immediate and longer-term effects of TBI depend on the mechanics of the injury and how this interacts with the structure of the brain, the skull, protective membranes, cerebrospinal fluid and blood supply. It is true that no two brains are alike, and no two impacts are alike, therefore there can be different effects from apparently similar impacts.

### *Primary damage*

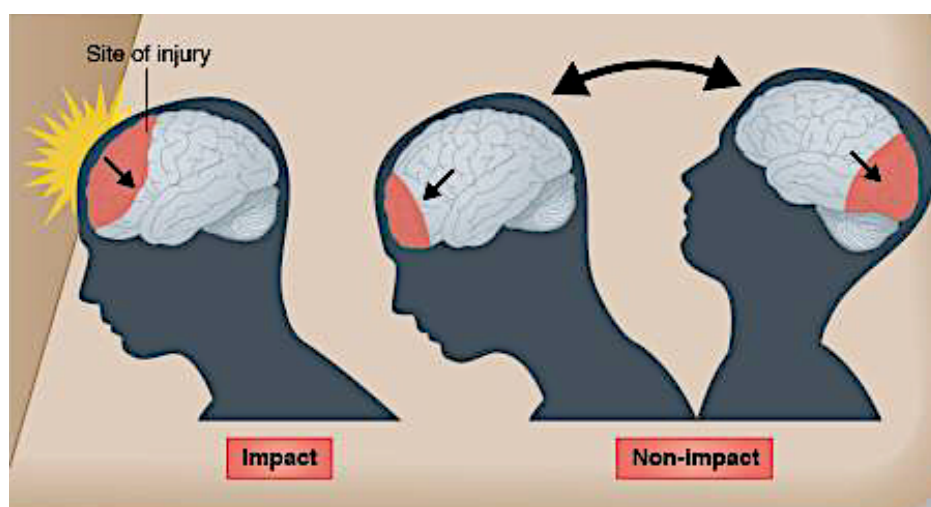
In TBI, there is a predilection for primary damage to the fronto-temporal regions of the brain because of the nature of the forces that typically apply to the brain in an accident (Lezak, 2004). For instance, in a transport accident the unrestrained occupant of a vehicle could be thrown forward and hit his/her head on a solid object (e.g. dashboard or windscreen) causing a direct blow to the forehead in an “impact” injury (see Figure 1). Alternatively, the brain could be subject to rapid deceleration when the person comes to a sudden halt, such as in the case of when a passenger in a vehicle is fully restrained by the seatbelt and airbags preventing the head hitting the dashboard or windscreen. The head might not suffer a direct hit but damage results from the brain moving in the skull and having impact with the sharp ridges of the sphenoidal bones.

Primary brain damage occurs due to bruising (referred to as *contusions*), diffuse axonal injury (DAI) and primary bleeding and blood clots (Powell, 2017). DAI is the straining and/or tearing that occurs at the moment of impact in which the nerve fibres, connections and

axonal sheaths are stretched and ruptured. Bleeding (referred to as *intracranial haemorrhage*) and blood clotting can cause collections of blood (referred to as *haematomas*) which then raise intracranial pressure further crushing the brain within the confines of the skull.

The blow at the point of impact is referred to as the *coup* and this is displayed as the red sections of the brains on the left and centre of Figure 1. There are corresponding *contrecoup* lesions as illustrated in red in the picture on the right of Figure 1, in which the brain sustains contusions opposite the area of the initial damage. In Figure 1 the brain has been exposed to lateral and rotational forces propelling it forward and down, and the contrecoup occurs because of the reaction to these forces from the brain which is sitting on the flexible brainstem immersed in cerebrospinal fluid. The physical forces are akin to the passengers of a bus being thrown forward as the bus brakes sharply, only to be thrown backwards when the bus comes to a halt. In Figure 1, the corresponding area is the occipital lobes but if the primary force was directed at another part of the brain, the corresponding area would change accordingly.

Figure 1: Types of Primary TBI. Arrows show the direction of the force applied to the brain.<sup>1</sup>



### Secondary damage

In the aftermath of TBI there are various threats to brain integrity due to secondary brain injury mechanisms as summarised by Ponsford, Sloan & Snow (2012). A key hazard is lack of blood and/or oxygen supply to the brain, referred to as *hypoxia* or *anoxia* caused by intracranial haemorrhage. There is threat to the brain due to swelling associated with *oedema* (i.e. fluid collection) and/or an increase in cerebral blood volume. Swelling reduces the flow of blood and oxygen to the brain and raises intracranial pressure (Powell, 2017). There is also a risk of blood collecting between the protective layer of the brain (the *dura mater*) and the surface of the brain causing a *subdural haematoma*. This might not be apparent in until some hours after the initial injury and can also result from injuries that seem unremarkable at the time (Shelat, 2018). All of these forms of swelling cause further damage by putting pressure on the brain with the resultant brain shift visible in imaging. When the brain swells, the patient might require *craniectomy* involving the temporary

<sup>1</sup> Source: Prins, Greco, Alexander, and Giza (2013). This is an Open Access article which permits unrestricted use, distribution and reproduction of material on the proviso that the original source is acknowledged.

removal of a part of the frontal skull bone. If the skull is fractured in the accident there is risk of infection (Powell, 2017) and also increased risk of hospital-borne infection that occurs with approximately 15% of craniotomies (Jiménez-Martínez et al., 2019). Finally, there can be delayed complications such as post-traumatic epilepsy (Verellen, & Cavazos, 2010) and *hydrocephalus*, which is an obstruction in the flow of cerebrospinal fluid usually treated by insertion of a shunt (Hu, Di, Shao, Zhou, & Jiang, 2018).

In the immediate aftermath there are pathophysiological changes which have been found using animal models of TBI. Prins, Greco, Alexander, and Giza (2013) have described neurochemical changes and metabolic changes. TBI directly disrupts cell membranes and leads to the redistribution of ions and neurotransmitters. In the first hour after TBI there is a massive release of glutamate which disrupts ionic equilibrium on post-synaptic membranes, referred to as “necrosis.” The amount of potassium released is proportionate to the severity of the impact and in order for neurons to fire again ionic equilibrium has to be re-established. Over the next few hours and days after a TBI there is a rise in intracellular calcium levels as part of a “cascade” of events which impairs mitochondrial function and prevents cell repair. This cascade of events includes changes in glucose metabolism in the brain such that there is an immediate increase in metabolism followed by a depression of glucose metabolism several days and weeks after a TBI, referred to as “apoptosis.” Studies of animal models and humans have shown that younger brains tend to return to normal glucose metabolism more quickly and therefore recover better from TBI.

In conclusion, TBI results in immediate and delayed physiological changes. The initial physical forces typically damage the fronto-temporal regions of the brain but can affect

other regions due to the vulnerability of the brain within its hard, protective skull. TBI sets off a complex sequence of events that may include swelling, infection, anoxia, secondary bleeding and cellular changes that lead to secondary brain damage.

### 1.2.2 Severity of TBI

The severity of TBI can be classified in different ways. At the time of injury, or in the early stages of recovery, TBI is classified by the duration and/or severity of loss of consciousness, typically as measured by the Glasgow Coma Scale (GCS; Teasdale & Jennett, 1974) and/or by the duration of PTA (Tate, 2012). The GCS comprises three item categories with scores allocated for eye opening, motor response or verbal response. Scores are summed and range from 3 (least responsive) to 15 (fully responsive). There are three categories of severity at this early stage: mild (GCS scores 13-15), moderate (GCS scores 9 - 12) or severe (GCS  $\leq$  8; Tate, 2012). There is an additional classification of mild-*complicated* TBI which refers to GCS of 13-15 accompanied by an intracranial bleed or lesion. Patients with 'mild-complicated' TBI have been shown to suffer worse cognitive effects and take longer to recover than patients with just the 'mild' specifier of TBI (Griffen & Hanks, 2014). GCS can be a helpful guide to early care and a good indicator of early and long term outcome from TBI however there is controversy about which score to use (score at admission to hospital or lowest/highest scores) and GCS scoring can be confounded by the early medical management of TBI, for instance when the patient is intubated and sedated. Coma duration has also been used as a predictor of longer-term outcome however it has similarly been shown to be inaccurate because of confounding variables (Sherer, Struchen, Yablon, Wang, & Nick, 2008).

The length of PTA is a better predictor of long-term outcome than coma duration (Walker et al., 2018), albeit there is substantial variance in outcome and mitigating factors include pre-injury functioning, previous concussions, demographic factors and social supports (Griffen & Hanks, 2014). In Australia<sup>2</sup>, duration of PTA is commonly measured with the Westmead PTA scale (Shores, Marosszeky, Sandanam, & Batchelor, 1986) which requires the patient to correctly recall 12 items reflecting orientation and new learning. This is administered daily, or hourly in cases of mild TBI. The duration of PTA is measured as the time since the TBI until the first of three trials with correct recall. Duration of PTA can be used to categorise the severity of TBI with less than one hour classified as “mild”, one to 24 hours classified as “moderate” and patients with one to seven days of PTA labelled “severe”. As noted by (Roebuck-Spencer & Cernich, 2014), many TBI patients have longer PTA durations and so one-to-four weeks PTA is classified as “very severe” and greater than four weeks PTA is classified as “extremely severe”.

### 1.2.3 Rates of TBI

Almost 7,000 people in the state of New South Wales, Australia alone are hospitalised each year following head trauma that involves some loss of consciousness, an incidence of 99/100,000 population (Pozzato, Tate, Rosenkoetter, & Cameron, 2019). Figures presented in Ponsford, Sloan, & Snow (2012) show that rates of TBI reported in Australian studies are

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<sup>2</sup> Other countries, e.g. USA, use the Galveston Orientation and Amnesia Test (GOAT; Levin, O'Donnell & Grossman, 1979). This is a 10-item scale, but some items have multiple components, making 14 questions and an additional two probing questions. The items cover orientation (autobiographical details, place and time) and historical memories to construct an estimate of the length of retrograde and anterograde amnesia.

somewhere in the mid-range with incidence varying such that some countries (e.g. South Africa) have up to 300/100,000 whereas Chinese figures are 56/100,000. However, Pozzato et al. noted “considerable methodological differences” in study design that prevent reliable comparisons in incidence across different countries. Most people admitted to hospital with TBI sustain mild injuries and go on to make a good recovery. Pozzato et al. reported that of the 6,827 hospitalised TBI cases in New South Wales in the 2007 calendar year, severity data were available for 2,925: 88% (n=2,580) sustained mild TBI, 8% (n=223) moderate, and 4% (n=122) had severe TBI.

In relation to the prevalence of TBI, the Australian statistics do not differentiate TBI from other forms of acquired brain injury (ABI) and date back data from the 1993 national census. This found approximately 1.9% of the Australian population (n = 338,700) self-reported that they were living with the ongoing effects of ABI (Australian Institute of Health and Welfare, 1999). Zaloshnja, Miller, Langlois, and Selassie (2008) estimated approximately 1.1% of the U.S. non-military population was living with TBI, which equated to between 3.17 and 3.22 million people. This estimate was based on calculations combining hospital separations with survival rates.

For many with severe TBI (PTA greater than one week) there is ongoing disruption to their cognitive and behavioural functioning (Griffen & Hanks, 2014), emotional coping (Anson & Ponsford, 2006), and there may be additional problems such as chronic pain (Irvine & Clark, 2018) or problems with motor-sensory function (Row et al., 2019). Moderate to severe TBI is associated with double the rate of cardio-vascular disease, triple the rate of endocrine dysfunction, more than double the rate of musculo-skeletal and rheumatologic disorders



and five times the rate of sleep disorders compared to large scale population studies (Hammond et al., 2019).

#### 1.2.4 Prognostic factors

Long term outcome from TBI depends on a variety of factors. It is not necessarily the case that a person with a severe injury has a poor outcome (Tate, Strettles, & Osoteo, 2003).

Tate, Lulham, Broe, Strettles, and Pfaff (1989) found almost half of a community sample of people with very severe TBI (PTA > 1 month in 74%) and who were on average six years post-injury were classified as “good recovery” on the Glasgow Outcome Scale (GOS; Jennett, & Bond, 1975 ). Similar outcomes have been found more recently, with a majority of moderate to severe TBI patients demonstrating “good recovery” on the GOS (Oppelt et al., 2018).

With reference to injury factors, duration of PTA has been found to be the only indicator that is consistently associated with outcome from TBI up to 5 years post-injury (Fraser, Downing, Biernacki, McKenzie, & Ponsford, 2019; Walker et al., 2018). Injury factors that were not predictive included initial GCS score, imaging findings, elevated intra-cranial pressure, cranial surgery and length of stay in the acute hospital. Length of stay in post-acute rehabilitation is associated with outcome depending on the severity of the injury, such that patients with a moderate injury benefit from at least 90 days of post-acute rehabilitation and patients with severe injuries benefit from at least 180 days of post-acute rehabilitation (Ashley, et al., 2018).

Initial severity markers are less predictive of outcome in the longer-term than demographic factors, which become more important factors over time. For example, age at time of injury has emerged as an important demographic factor that has been shown to influence outcome such that at one-year post-injury better cognitive recovery is associated with younger age (Rabinowitz, Hart, Whyte, & Kim, 2018). Schönberger, Ponsford, Olver, Ponsford, and Wirtz (2011) conducted structural equation modelling in order to predict functional recovery and employment outcomes for 949 people one-year after moderate-to-severe TBI. They found that age, education, the nature of pre-injury employment, injury severity factors, and comorbid limb injuries were direct predictors of employment outcomes. Gender, pre-injury psychiatric disorders and limb injuries were associated with mood, cognitive and behavioural changes. At five years post-injury, premorbid education, productivity or occupation (Walker et al.) and premorbid intelligence (Fraser et al.) have been shown to be predictive of outcomes. Draper, Ponsford, and Schönberger (2007) examined factors that influence psycho-social outcomes at 10 years post-injury, as measured by the Sydney Psychosocial Reintegration Scale (SPRS; Tate, Hodgkinson, Veerabangsa, & Hodgkinson, 1999). Duration of PTA was the strongest predictor of overall SPRS score when this was rated by the relatives of TBI patients. When people with TBI rated themselves, the predictors of overall outcome were more related to factors such as subjective reports of fatigue, depression and anxiety. This finding emphasises the importance of interventions for the sequelae of TBI and depression in particular.

### 1.2.5 Sequelae of TBI

As noted above, changes caused by TBI can be temporary and/or permanent, and affect a range of functions (Tate, 2012). Such changes can be described in the context of the International Classification of Functioning, Disability and Health (ICF; World Health Organization, 2001) as recommended by Tate and Perdices (2008). The ICF is a framework for measuring health and disability that allows for precise descriptions of health outcomes. The components are listed in Table 1 along with their definitions and code prefixes. The sequelae of TBI are discussed below with the ICF alphanumeric code included in parentheses. When the ICF code label does not clearly match the text, the label is included in inverted commas.

Long term outcome from TBI is most often associated with changes in cognitive processes, most particularly information processing speed or “pace of thought” (b1600), attention and concentration (b140), and memory (b144). TBI, as discussed by Cicerone and Maestas (2014), typically involves damage to the frontal lobes (s11000), and thus is often associated with disruption of executive functions (b164) such as problem solving (b1646) and planning (b1641); disorders of drive (b1300) and motivation (b1301), presenting as apathy (Lane-Brown & Tate, 2009), or changes in affect, displayed as either flatness or elevation/euphoria (Tate, 2012); problems with the regulation of emotions (b1521) can present as immaturity, egocentricity, irritability and/or changes in libido (b6400). Frequently people with TBI present with deficits in social function (b122), contributed to by impairments in emotion perception, social cognition and social problem-solving. These have been found to be associated white matter changes found in patients several years following a TBI (McDonald,

Dalton, Rushby, & Landin-Romero, 2019). Severe TBI often leads to an impairment of insight (b1644) and can present as denial of, or compromised concern about, cognitive impairments. This might cause people with severe TBI to have unrealistic plans or timeframes for their recovery. There may also be the issue of “defensive denial” in which a pre-injury personality style associated with of perfectionism and/or difficulty in acknowledging personal failings leads to denial and/or minimisation of the existence of TBI-related impairments in order to protect their self-concept (Ownsworth, 2005).

Table 1: Components of the ICF

<b>Component</b>	<b>Definition</b>	<b>Code prefix</b>
<b>Body functions</b>	Physiological functions of body systems, including psychological functions	b
<b>Body structures</b>	Anatomical parts of the body such as organs, limbs and their components	s
<b>Activity/Participation</b>	Includes “activity”, the execution of tasks or actions and “participation”, which is involvement in life situations	d
<b>Environmental factors</b>	The physical, social and attitudinal environment in which people live and conduct their lives	e
<b>Personal factors</b>	The particular background of an individual’s life and living which is not part of health status, e.g. gender, race, education, lifestyle or individual psychological assets.	not yet classified within the ICF

Another characteristic impairment after severe TBI is impaired behavioural regulation (d720). This can be one of the most difficult personality changes following TBI and has an impact on families, support and accommodation providers, as well as within the context of the criminal justice system (e5500). Of the referrals to a state-wide specialist behavioural support service in Victoria, Australia Kelly and Parry (2008) found the most common categories of challenging behaviours following TBI were (in order of prevalence) verbal aggression and physical aggression (d7202), social inappropriateness (d7102 “showing tolerance” or d7203 “verbal/physical regulation”), lack of initiation (b1301 “apathy”), inappropriate sexual behaviour expressed verbally or physically (d7207), wandering or absconding (cf. b114 “orientation” or b1478 “psychomotor functions, other specified”), and perseverative/repetitive behaviours (b1601 “form of thought” or b7653 “stereotypies and motor perseveration”). Only a small proportion of people with severe TBI demonstrate challenging behaviours, for instance the point prevalence of inappropriate sexual behaviour is less than 9% (Simpson, Sabaz, & Daher, 2013), however this has a disproportionate impact on the community connected to such cases.

Finally, TBI can cause various sensory and/or motor impairments due to damage to the part of the brain relevant to those functions (Ponsford et al., 2012). For instance, the olfactory bulb is vulnerable and if damaged it leads to changes in sense of smell (b1562) and taste (b1563). Similarly, damage to the optic nerve or visual cortex can lead to visual problems (b210) such as diplopia (double vision) or visual field deficits. Damage to the motor cortex can lead to lateralised impairments in movement and dexterity (b760, e.g. ataxia), and strength or control (b730, e.g. hemiparesis). It is common to have impairments in the domain of communication (d3) functions which might be related to motor control in speech

production, e.g. dysarthria (b320) or dyspraxia (d176) or have a cognitive basis (b3300) e.g. verbal generativity or pragmatic communication such as turn-taking in conversation.

In summary, there is a wide range of outcomes from TBI which can vary from mild and subtle impairments through to impairments of such severity that they cause profound disability. Function will depend on the nature of the injury and the extent of the person's recovery, which is moderated by contextual factors such as the person's environment and their personal resources. Because the brain has a role in all body systems there is not an area of physical, cognitive, behavioural, emotional or sensory function that is excluded from TBI, although some impairments are more common than others.

### **1.3 Depression**

Mood disorders are estimated to be between four and eight times more common after TBI than in the general population (Osborn, Mathias, & Fairweather-Schmidt, 2014). Major depressive disorder (MDD), as defined by the Diagnostic and Statistical Manual of the American Psychiatric Association, is a mood disorder in which there is at least one major depressive episode lasting for at least two weeks (American Psychiatric Association, 2013). Major depressive episodes are characterised by low mood or loss of interest in activities that are usually enjoyed. During these episodes there may be a loss of appetite, changes in weight, sleep disturbances, psychomotor agitation or retardation, low energy, fatigue, irritability, feelings of worthlessness or inappropriate guilt, difficulty concentrating, indecisiveness, and in more severe cases, persistent thoughts of death or suicide.

Depression occurs in children, adolescents, and adults, and can be associated with somatic

complaints or psychotic symptoms, such as delusions. Symptoms of depression, such as depressed mood or poor motivation, may co-occur with other mental conditions (e.g. adjustment disorder), or may be present without meeting criteria for any specific diagnosis (National Institute for Health Care Excellence, 2013).

Bombardier et al. (2010) tracked the recoveries of 599 consecutively-admitted patients to a Level 1 trauma centre in Seattle, USA in the year following complicated-mild to severe TBI. More than half of the sample fulfilled diagnostic criteria for MDD during the first 12 months post-injury. Major depressive episodes can occur, re-occur or persist for many years post-TBI and it is estimated that over first 5 years following TBI approximately 40% of people will suffer from a major depressive episode (Osborn et al., 2014) and this could contribute to a diagnosis of MDD or another mood disorder (e.g. bipolar disorder).

To complicate diagnosis, some common symptoms of TBI overlap with depression including insomnia and chronic fatigue (Ouellet, Beaulieu-Bonneau, & Morin, 2006), and apathy (Lane-Brown & Tate, 2009). Depression is also associated with impairments in cognition. Difficulty with concentration is a diagnostic criterion according to DSM-5 and people with depression have been found to have slightly reduced performance on measures of attention, verbal memory recall and mental flexibility (Airaksinen, Larsson, Lundberg, & Forsell, 2004; Gorwood, Corruble, Falissard, & Goodwin, 2008).

### 1.3.1 Aetiology of depression post-TBI

The development of depression post-TBI can be a direct consequence of neurological changes in the brain, and/or a secondary reaction to significant impairments and life changes (Moldover, Goldberg, & Prout, 2004), and/or or may be a reflection of injured persons' coping styles (Anson & Ponsford, 2006). Alway, Gould, Johnston, McKenzie, and Ponsford (2016) found increased risk for those who had a history of depression prior to TBI. Bombardier et al. (2010) also found increased risk for those who had a depression at the time of the injury and/or a history of alcohol dependence prior to TBI.

Bhalerao et al. (2013) reviewed the literature relating to post-TBI neuropsychiatric disorders giving greater weight to studies that were more recent and had higher methodological quality. They concluded that depression post-TBI was more often associated with damage to the neocortex and associated white matter, left dorso-lateral frontal cortex, the basal ganglia (striatum, thalamus), hippocampus and the raphe nucleus. The primary neurotransmitters involved were serotonin, norepinephrine and dopamine. They reported the finding that frontal contusions increase the risk of suicide, due to significant associations between decreased white matter integrity, suicidal ideation and impulsive behaviour. These findings do have implications for the common clinical questions asked in this thesis, particularly whether treatments developed for non-brain-impaired populations are applicable when there is an organic basis to the mood disorder.



### 1.3.2 Models of depression

There are several models concerned with the development of depression. Modern theories of the aetiology of depression attempt to integrate biological, psychological and social influences (Friedman, 2014). Current conceptualisations of depression have been influenced by Kandel (1998) who was famous for his Nobel-prize winning research showing how learning in simple organisms led to observable changes in neurophysiology. Kandel stated that “all functions of mind reflect functions of brain” (p. 460) and that “genes contribute importantly to mental function and can contribute to mental illness” (p. 462). He concluded that experiences, learning and stressors can influence gene expression and neuronal connections. He posited that psychotherapy and pharmacotherapy may also lead to structural changes in the brain. This model of depression fits well within the context of the structural and neurochemical changes in TBI.

Cognitive models of depression (e.g. Beck, 1979) link *depressogenic* thinking styles, in which there is a set of maladaptive core thoughts, to negative, self-defeating self-talk. This reflects a lack of psychological resilience such that when a catastrophic event (such as a TBI) occurs the patients suffers demotivation. TBI can cause significant changes in life roles and functions that the individual is able to pursue. Moderate-to-severe TBI will require a period of hospitalisation followed by weeks or months of rehabilitation, removing patients from their usual lives. For patients in the range of extremely severe injuries, adjustment to disability can be a lifelong challenge (Tate et al., 2003). When these challenges occur within the context of a depressogenic thinking style, depression can ensue.

Another popular model of depression is that of *learned helplessness* pioneered by the work of Seligman who conducted research in which his canine participants were unable to avoid terrifying electric shocks. Initially they reacted with distress and tried to escape but eventually they gave up and froze, succumbing to helplessness and hopelessness (Seligman, 1992). This model appears to fit well with the experience of acquired disabilities where it seems that despite efforts towards recovery, the injured person may not manage to restore all of the functional ability and self-perceived status that he/she enjoyed pre-injury. This is often aided by inaccurate reminiscence about his/her earlier life, creating a dichotomy between life before and life after the accident.

As discussed in the foregoing, people with TBI may have poor insight or limited self-awareness of their deficits, or in fact develop defensive denial as a coping mechanism to changed circumstances (Ownsworth, 2005). There has been some debate about the influence of impaired self-awareness with Malec, Testa, Rush, Brown, and Moessner (2007) finding that it may serve as a barrier to prevent the development of depression. From the author's experience of conducting psychological therapies with TBI clients over many years, he is aware that as clients develop increased insight into their TBI-related impairments they experience grief and loss, which can be reflected in deteriorations in mood. The benefit, or otherwise, of reduced insight and defensive denial was discussed by Ownsworth (2005). She noted that denial might be protective in the early stages of recovery, but may lead to much worse adjustment and ultimately to "extreme emotional reactions that are particularly related to themes of separation and loss" (p. 85). She concluded that in order to promote positive adjustment to TBI it is better to develop insight and learn to cope with impairments. Interventions such as Acceptance and Commitment Therapy (ACT) aim to

increase acceptance of impairments in order to foster adjustment following TBI (Whiting, Deane, McLeod, Ciarrochi, & Simpson, 2019). This is consistent with the earlier model of depression following TBI put forward by Prigitano (1991) who highlighted the loss of identity that comes with cognitive and functional impairments and the need to find meaning in life following TBI.

To summarise, the model of depression in non-neurological populations identifies both biological and psychological aetiological factors. In TBI cases, there is a combination of organic structural and neurochemical changes, as well as secondary adjustment issues. Depending on the nature of the injury and the person's coping resources, depression can result. This occurs in some, but not all cases, as discussed below.

### 1.3.3 Clinical Course

Alway et al. (2016) conducted a prospective study of 161 admissions to hospital with moderate to severe TBI. Participants were assessed at three, six and 12 months and then every year for up to five years post-TBI. This was an Australian sample with similar characteristics to participants in studies reported in this thesis. Alway and colleagues found that the most common psychological presentations after moderate to severe TBI were anxiety, mood and substance abuse disorders. In the first year, the rate of mood disorders (most commonly MDD) was 40.1% dropping to 27.7% by the fifth year post-TBI. Most people with mood disorders post-TBI had not had a mood disorder pre-TBI, however the history of a mood disorder pre-TBI almost doubled the likelihood of depression post-TBI. Most mood disorders were diagnosed within the first year post-TBI but there was a

substantial proportion of cases experiencing their first diagnoses in the second- or third-year post-injury. The rates of mood disorders were not significantly related to injury or demographic variables, but Alway et al. noted that development of psychiatric disorders was associated with age at injury (less likely after age 30) and the presence of a limb injury causing pain or further disability. Mood disorders typically co-occurred with anxiety disorders in the first year. These findings were consistent with previous studies which found elevated rates of depression in the first year post-injury (Bombardier et al., 2010; Ciurli, Formisano, Bivona, Cantagallo, & Angelelli, 2011) and up to 5 years post-injury (Dikmen, Bombardier, Machamer, Fann, & Temkin, 2004). Aside from diagnosable major depressive disorder there are many TBI patients that experienced sub-clinical minor depression. Hart et al. (2011) assessed a very large TBI Model Systems cohort (N=1,570) and found that one year post-TBI 26% reported major depression and 22% reported minor depression.

#### 1.3.4 Impacts of post-TBI depression

According to the Australian Burden of Disease Study, depression and suicide (with associated self-inflicted injuries) are conditions with high burden on society in terms of effective years lost (Australian Institute of Health and Welfare, 2015). Depression and anxiety can limit recovery from TBI (Whitnall, McMillan, Murray, & Teasdale, 2006). This is because mood and anxiety disorders impact negatively on cognitive function and also because they may affect motivation towards rehabilitation activities which is associated with lower participation in rehabilitation activities.

There is a doubled risk of mortality from suicide following TBI. Hostetter et al. (2019) studied the rates of suicide occurring in military veterans, making comparisons between veterans with history of no TBI, mild TBI and moderate/severe TBI. Drawing upon the medical histories of over 1.4 million military veterans, they found the chance of suicide increased by more than one-and-a-half times following mild TBI and by more than double following moderate or severe TBI. This is an important finding as it is presumed that all groups of veterans would be exposed to similar conditions in the course of their service, although they did find the TBI groups were younger than the non-TBI groups, and so age could be a risk factor as well. Hostetter et al. found that 67.3% of veterans with TBI had a diagnosis of depression or unipolar mood disorder prior to their deaths, representing a doubling in the prevalence of depression in veterans who had died by suicide. Apart from military samples, Simpson and Tate (2002) found that in a community sample of brain injured outpatients in Sydney, 18% had made a suicide attempt since their injury, and 35% had clinically significant levels of suicidality. Furthermore, Simpson and Tate found that post-injury emotional disturbance (including the presence of depression) was a stronger predictor of suicidality than pre-injury emotional disturbance or history of suicide attempts.

Finally, a multi-centre study of patients with MDD found that patients with a history of two or more suicide attempts had higher levels of depression, impulsivity, substance abuse and aggression (Coryell et al., 2018). This study did not report whether participants had any history of brain impairment, however it did find mood and behavioural features common in TBI were associated with suicide attempts. This study underlines the importance of treating depression along with behavioural disorders (impulsivity and aggression) and substance use disorders.

### 1.3.5 Current interventions for depression post-TBI

Interventions for post-TBI depression are broadly divided into pharmacological and non-pharmacological. It is readily apparent that for a neurological condition such as TBI, where there is a range of physiological changes that could affect mood, from the moment of impact to secondary processes continuing long after injury, that pharmacotherapy might be of benefit. A recent systematic review by Slowinski, Coetzer, and Byrne (2019) found a range of pharmacological agents were administered to patients with depression following TBI. These include selective serotonin reuptake inhibitors (e.g. sertraline or citalopram), tricyclic antidepressants (e.g. desipramine or amitriptyline), monoamine oxidase inhibitors (e.g. phenelzine), or psychostimulants (e.g. methylphenidate). Pharmacotherapy may be applied proactively to prevent the development of depression post-TBI or after diagnosis of depression, however the evidence in support of pharmacotherapy is mixed with no clear benefit for preventing (Clay et al., 2019) or treating depression (Slowinski et al.).

Non-pharmacological interventions are the subject of a Cochrane systematic review in this research program (Gertler, Tate, & Cameron, 2015) and are discussed in depth in Chapter 2. Interventions include psychological therapies, such as CBT or acceptance and commitment therapy, as well as behavioural interventions, such as exercise programs. There are also non-pharmacological medical interventions such as surgeries or physical treatments such as brain stimulation.

In summary, depression is more prevalent among people who have had TBI, compared to the general population without brain impairment. Depression treatments have been evaluated with non-brain-impaired samples and it is unknown whether these treatments are applicable to people with TBI-related changes in cognition, communication, emotion regulation and/or behaviour. This research program set out to determine whether psychological and other non-pharmacological interventions could effectively treat depression following TBI.

#### **1.4 Aims of thesis**

This thesis documents an integrated program of research that was devised in order to answer those common clinical questions raised at the beginning of this chapter. The thesis consists of four studies, each of which can be read as individual reports, but are connected to the thesis aims. Three studies (Chapters 2, 3 and 5) have been published already. A fourth study is currently under review after having been re-submitted following an initial round of reviewer feedback which was “in general favourable and suggest[ed] that, subject to minor revisions, [the] paper could be suitable for publication.” (Chapter 4). The specific aims for each study are discussed below:

- (a) Study 1 (Chapter 2; Gertler et al., 2015): To identify the available evidence regarding non-pharmacological interventions for depression following TBI. This took the form of a Cochrane systematic review which identified evidence from randomised controlled trials (RCTs) with the following aims:
  - a. Identify published and non-published RCTs of interventions.

- b. Evaluate the methodological quality of the available studies.
- c. If possible, to combine datasets into meta-analyses.
- d. Provide analyses of treatment effects of identified interventions.
- e. Provide overall analyses of interventions which combined their rated quality with treatment effects in order to assist researchers and clinicians in selecting interventions.

(b) Study 2 (Chapter 3; Gertler & Cameron, 2018): To elucidate the statistical analyses used in Cochrane reviews in order to assist clinicians and researchers in understanding the results, conclusions and recommendations provided by Cochrane reviews, using Study 1 as a reference.

(c) Study 3 (Chapter 4; Gertler & Tate, 2020): To develop a valid method of determining the impact of treatment on mood of people with TBI. Group studies tend to rely upon standardised outcome instruments (symptom checklists and diagnostic instruments) administered pre- and post-intervention. However, clinicians and researchers require a measure of mood that can be conveniently applied throughout the course of treatment to track progress. In clinical practice, practitioners sometimes use single-item mood scales (SIMS) in order to determine patients' responsiveness and to guide treatment. The aim of Study 3 was to determine the validity of SIMS, delivered verbally or visually, for tracking the mood of patients with TBI.



(d) Study 4 (Chapter 5; Gertler & Tate, 2019): To select and evaluate an intervention to improve participation and mood in people with depression post-TBI. Following from the recommendations of the Cochrane review, the aim was to determine whether a behavioural activation intervention could lead to demonstrated improvements in mood and activity participation in a Phase 1 single-case experimental design (SCED) study.

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## CHAPTER 2

### Section 1

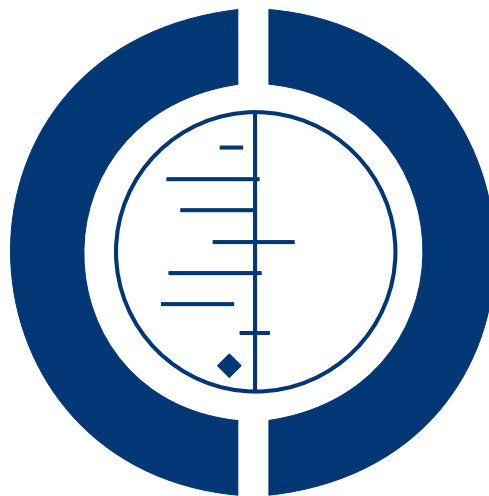
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# Non-pharmacological interventions for depression in adults and children with traumatic brain injury (Review)

Gertler P, Tate RL, Cameron ID



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[Intervention Review]

# Non-pharmacological interventions for depression in adults and children with traumatic brain injury

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## ABSTRACT

### Background

Following traumatic brain injury (TBI) there is an increased prevalence of depression compared to the general population. It is unknown whether non-pharmacological interventions for depression are effective for people with TBI.

### Objectives

To investigate the effectiveness of non-pharmacological interventions for depression in adults and children with TBI at reducing the diagnosis and severity of symptoms of depression.

### Search methods

We ran the most recent search on 11 February 2015. We searched the Cochrane Injuries Group Specialised Register, *The Cochrane Library*, MEDLINE (OvidSP), Embase (OvidSP), three other databases and clinical trials registers. Relevant conference proceedings and journals were handsearched, as were the reference lists of identified studies.

### Selection criteria

Randomised controlled trials (RCTs) of non-pharmacological interventions for depression in adults and children who had a TBI.

### Data collection and analysis

Two authors independently selected trials from the search results, then assessed risk of bias and extracted data from the included trials. The authors contacted trial investigators to obtain missing information. We rated the overall quality of the evidence of the primary outcomes using the GRADE approach.

### Main results

Six studies met the inclusion criteria, with a total of 334 adult participants. We identified no studies that included children as participants. All studies were affected by high risk of bias due to a lack of blinding of participants and personnel; five studies were affected by high risk of bias for lack of blinding of outcome assessors. There was high or unclear risk of biases affecting some studies across all the Cochrane risk of bias measures.

Three studies compared a psychological intervention (either cognitive behaviour therapy or mindfulness-based cognitive therapy) with a control intervention. Data regarding depression symptom outcome measures were combined in a meta-analysis, but did not find an

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**Non-pharmacological interventions for depression in adults and children with traumatic brain injury (Review)**

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effect in favour of treatment (SMD -0.14; 95% CI -0.47 to 0.19;  $Z = 0.83$ ;  $P = 0.41$ ). The other comparisons comprised of single studies of depression symptoms and compared; cognitive behaviour therapy versus supportive psychotherapy (SMD -0.09; 95% CI -0.65 to 0.48;  $Z = 0.30$ ;  $P = 0.77$ ); repetitive transcranial magnetic stimulation plus tricyclic antidepressant (rTMS + TCA) versus tricyclic antidepressant alone (SMD -0.84; 95% CI -1.36 to -0.32;  $Z = 3.19$ ,  $P = 0.001$ ); and a supervised exercise program versus exercise as usual (SMD -0.43; 95% CI -0.88 to 0.03;  $Z = 1.84$ ;  $P = 0.07$ ). There was very-low quality evidence, small effect sizes and wide variability of results, suggesting that no comparisons showed a reliable effect for any intervention.

Only one study mentioned minor, transient adverse events from repetitive transcranial magnetic stimulation.

### Authors' conclusions

The review did not find compelling evidence in favour of any intervention. Future studies should focus on participants with a diagnosed TBI and include only participants who have a diagnosis of depression, or who record scores above a clinical cutoff on a depression measure. There is a need for additional RCTs that include a comparison between an intervention and a control that replicates the effect of the attention given to participants during an active treatment.

## PLAIN LANGUAGE SUMMARY

### Non-drug treatments for depression in children and adults who have had a traumatic brain injury

#### Review question

We reviewed the evidence about the effect of non-drug treatments for depression after traumatic brain injury (TBI), to determine whether these treatments are better than no intervention, or better than drug-based treatments, at reducing the symptoms or diagnosis of depression. We searched for evidence about the relative effectiveness of different types of treatments, and whether the treatments had any harmful or negative effects.

#### Background

Depression is more common in people who have had a TBI. Depression increases the risk of suicide and is a factor that limits recovery from TBI. There are many non-drug treatments for depression. This review aimed to determine the effects of non-drug interventions for people with TBI.

#### Search date

The review authors searched for randomised studies that had been published up to February 2015.

#### Study characteristics

We found six studies, with a total of 334 adult participants. We found no studies that included people younger than 18 years of age. Four studies investigated psychological interventions. One study investigated an exercise intervention, and another investigated repetitive transcranial magnetic stimulation (rTMS).

#### Key results

Three studies compared a psychological therapy (cognitive behaviour therapy or mindfulness-based cognitive therapy) with a no-treatment control intervention. When the data for these studies were combined, there was no reliable effect in support of psychological therapy. One study compared cognitive behavioural therapy with another psychological intervention (supportive psychotherapy), and did not find an effect in favour of either intervention. One study compared a supervised exercise programme with exercise as usual, but did not find an effect in favour of either intervention. One study compared rTMS plus an antidepressant medication with the antidepressant medication alone. Because the quality of the evidence was very low, it was not possible to draw the conclusion that the addition of rTMS improved outcomes. Only one study, of rTMS, reported any harmful effects and these were relatively minor and resolved quickly.

#### Quality of the evidence

The quality of the evidence was rated very low. All studies were at high risk of bias in some ways, and therefore it was not possible to draw conclusions in support of any intervention. There was a high degree of variability in the main results, which meant we could have little confidence in the findings. Some studies had major methodological flaws.

**Conclusions**

It is not possible to recommend any particular treatment based on the current evidence. The review authors have made some recommendations to improve the quality of the evidence in future studies.

**SUMMARY OF FINDINGS FOR THE MAIN COMPARISON** *[Explanation]*

CBT compared to wait-list control for post-TBI depression						
<b>Patient or population:</b> Post-TBI depression <b>Settings:</b> Community setting <b>Intervention:</b> CBT <b>Comparison:</b> Wait-list control						
Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	wait-list control	CBT				
Depression scales (BDI-II, HAM-D and HADS); higher score means more depressed	The mean depression score in the control groups was 15.36 <sup>4</sup>	The mean depression score in the intervention groups was 0.14 standard deviation lower (0.47 lower to 0.19 higher)	SMD -0.14 (-0.47 to 0.19)	146 (3 RCTs)	⊕○○○ VERY LOW <sup>1,2,3</sup>	
*The basis for the <b>assumed risk</b> (e.g. the median control group risk across studies) is provided in footnotes. The <b>corresponding risk</b> (and its 95% confidence interval) is based on the assumed risk in the comparison group and the <b>relative effect</b> of the intervention (and its 95% CI). <b>CI:</b> Confidence interval;						
GRADE Working Group grades of evidence <b>High quality:</b> Further research is very unlikely to change our confidence in the estimate of effect. <b>Moderate quality:</b> Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate. <b>Low quality:</b> Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate. <b>Very low quality:</b> We are very uncertain about the estimate.						

<sup>1</sup>Of these three studies, there is variability in the quality of the evidence as it relates to risks of bias. [Bedard 2013](#) had serious risk of bias as it related to random sequence generation (selection bias) and incomplete outcome data (attrition bias). [Simpson 2011](#) suffered from other risks of bias due to a very small sample size. All three studies (including [Fann 2015](#)) were subject to biases that are virtually unavoidable when attempting an RCT on this topic. All studies suffered from lack of blinding as it relates to participants and personnel (performance bias) and blinding of outcome assessment (detection bias).

<sup>2</sup>Small effect sizes. Two studies slightly favour CBT ([Bedard 2013](#); [Fann 2015](#)). One study slightly favours control ([Simpson 2011](#)).

<sup>3</sup>The 95% confidence interval of the outcome is very broad and ranges from a moderate effect in favour of CBT to a small effect against CBT.

<sup>4</sup> The assumed risk was calculated by adding the means of the scores of the control groups and dividing by the number of studies in the analysis.

## BACKGROUND

### Description of the condition

Major depression is defined by at least one episode of either depressed mood or loss of interest and pleasure in usual activities (or both) consistently for at least a two-week period. During depressive episodes there can be a loss of appetite, weight (or both), insomnia, psychomotor agitation or retardation, low energy, fatigue (or both), feelings of worthlessness, inappropriate guilt (or both), difficulty concentrating, indecisiveness, and in more severe cases, persistent thoughts of death or suicide. Depression can affect children, adolescents, and adults, and can be associated with somatic complaints, psychotic symptoms, such as delusions, or both (APA 2000). In addition, depressive symptoms, such as depressed mood or poor motivation, may co-occur with other mental conditions (e.g. adjustment disorder), or may be present in the absence of a diagnosable condition (NICE 2009).

Traumatic brain injury (TBI) is a heterogeneous condition that can affect people of any age. The common factor in all presentations is that damage to the brain occurs because of external forces, such as direct impact, rapid acceleration or deceleration, a penetrating injury, or blast waves from an explosion. These external forces can vary greatly along parameters of intensity, location, direction, and duration and determine the nature of the injury (Maas 2008). The immediate impact of the trauma leads to a disruption in the neurological function of the brain in any of the following ways: i) loss of consciousness, ii) loss of memory for events immediately before or after the injury, iii) a change in mental state at the time of the injury, or iv) permanent or transient focal neurological deficits (Kay 1993).

Traumatic brain injury is associated with a combination of temporary or permanent changes in cognitive abilities, emotional regulation, and behavioural control (Maas 2008). Traumatic brain injury can vary in severity and is classified as mild, moderate, severe, or extremely severe. It can also result in physical impairments and functional disabilities.

Following TBI, there is an increased occurrence of depression compared with the general population. Bombadier 2010 found that 53.1% of a hospital sample met the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) diagnostic criteria for major depressive disorder in a 12-month period after suffering TBI. This is in contrast to a general population survey which found that the 12-month prevalence of all mood disorders was 6.2% (Slade 2009).

In a prospective study, it was found that the prevalence of moderate to severe symptoms of depression ranged from 31% at one month, to 17% at three to five years post-injury (Dikmen 2004). There was little relationship between brain injury severity and symptoms of depression. When people with TBI were rated by their relatives, a similar frequency of depression was found (Ciurli 2011). Compared with the general population, there is an increased risk

of emotional disorders in children and adolescents following TBI, with a recent study finding that half of a sample of eight- to 15-year olds presented with symptoms of an internalising disorder, and that as a group, they displayed elevated scores on ratings of anxiety, depression, and social withdrawal (Poggi 2005).

Depression is a relevant condition to investigate because it represents a significant risk factor for mortality through suicide. Simpson 2002 found that in a community sample of brain injured outpatients in Australia, 18% had made a suicide attempt since their injury, and 35% had clinically significant levels of suicidality. Furthermore, Simpson 2002 found that post-injury factors had greater significance than pre-injury emotional disturbance (including previous suicide attempts) in predicting suicidality post-injury, so it was changes associated with TBI that had led to increased suicide risk.

### Description of the intervention

Interventions for depression can be pharmacological, non-pharmacological, or a combination (NICE 2009). Because there is already a Cochrane review in preparation which focuses on pharmacological interventions (Vattakatuchery 2013), this review will focus on non-pharmacological interventions. These are predominantly psychological interventions, but also include medical, physical, or other interventions. Psychological interventions include those that are behavioural, cognitive, or a combination (cognitive-behavioural therapy (CBT)). There are extensions of CBT which are referred to as 'third-wave' interventions; these include mindfulness, acceptance, and commitment therapy (ACT), and dialectical behaviour therapy (DBT). There are also the separate schools of humanistic, interpersonal, and psychodynamic psychotherapies. Non-pharmacological medical interventions include electroconvulsive therapy (ECT), repetitive transcranial magnetic stimulation (rTMS), neurosurgical interventions, and biofeedback. Physical interventions include exercise programmes and other physical activation strategies. There are also complementary and alternative medicine (CAM) interventions, which include the administration of herbal supplements, traditional Chinese medicine, homeopathy, acupuncture, and other interventions.

### How the intervention might work

Non-pharmacological interventions might work in a variety of ways, which reflect the heterogeneity of the interventions.

Psychological interventions, such as CBT, might work by training people with depression in strategies to manage their symptoms, such as learning to identify and challenge patterns of negative thinking. Psychological interventions may work in the TBI population similarly to the non-brain injured population and other clinical groups that have cognitive impairments or reduced ability to concentrate, remember or solve problems, such as children,

people with intellectual disabilities, or people with other types of acquired brain injuries such as stroke.

Medical interventions, such as TMS, might work by exciting or inhibiting cortical areas of the brain in order to manipulate mood. Physical interventions, such as exercise programmes, might work because of various reasons, for example, depression is often associated with inactivity, and exercise helps to increase activity levels and self-efficacy, and distract from negative thoughts. If successful, these treatments reduce the severity of depression symptoms and the rate of diagnosis of a major depressive disorder.

For the non-brain injured population, there is varying evidence in support of non-pharmacological interventions for depression. There is a series of Cochrane reviews that have either been recently published, or are in the protocol stage, that examine the effectiveness of specific psychological interventions in comparison with 'treatments as usual', or examine the relative effectiveness of treatments in comparison with other treatments. As an example, Churchill 2013 examined 'third wave' cognitive and behavioural therapies versus treatment as usual for depression, and found that these treatments were effective on a short-term basis, albeit there was insignificant evidence to state whether these treatments were any more or less effective than other psychological therapies (Hunot 2013). The same group has evaluated behavioural therapies and found that they were as effective as other treatments, albeit with a lack of high-quality evidence (Shinohara 2013). The same group has completed a Cochrane review that compared the effectiveness of psychological therapies versus antidepressant medication, alone and in combination, for depression in children and adolescents; however, there were no clear findings, suggesting that either mode of therapy, or a combination of both, is preferable (Cox 2012). And finally, the comparison between behavioural therapies and treatment as usual by the same team, is in the protocol stage (Caldwell 2010). Other reviews by the same group that are in the protocol stage relate to: cognitive-behavioural therapies (Churchill 2010a; Hunot 2010), humanistic therapies (Churchill 2010b; Davies 2010), interpersonal, cognitive-analytic, and other integrative therapies (Churchill 2010c; Hunot 2010a), and psychodynamic therapies (Churchill 2010e; Moore 2010).

Aside from psychological interventions, other modes of intervention examined by previous Cochrane reviews show that there is a lack of evidence in support of acupuncture (Smith 2010), or transcranial magnetic stimulation (Rodriguez-Martin 2001), and moderate support for light therapy (Tuunainen 2004), music therapy (Maratos 2008), and relaxation (Jorm 2008). A recent Cochrane review found a small effect in support of physical exercise interventions when compared with a no-treatment control, and no significant difference between psychological or pharmacological interventions and physical exercise in treating depression (Cooney 2013). Leiknes 2011 is currently investigating the benefits and harms of electroconvulsive therapy (ECT) for depression. For children and adolescents, two previous Cochrane reviews

found some evidence that indicated limited support for family therapy (Henken 2007), and exercise (Larun 2006), in the prevention and treatment of depression.

### Why it is important to do this review

As discussed above, the TBI population has a higher prevalence of depression in comparison with the general population (e.g. Deb 1999). Depression and anxiety might be factors that limit recovery from TBI (Whitnall 2006). Depression is one of the risk factors for increased risk of suicide after TBI (Simpson 2002).

Although depression is a significant problem following TBI, it is unknown whether non-pharmacological interventions are effective in the TBI population. In particular, people with TBI often have impairments of cognition, behavioural or emotional control, which affect the suitability of interventions that were developed for non-brain injured populations.

This review sought to determine the effectiveness of non-pharmacological interventions for depression when applied to the TBI population. Where interventions are successful, it is important to understand how these interventions were applied and what modifications were necessary for this population with cognitive impairments.

## OBJECTIVES

1. To determine whether non-pharmacological interventions (either with or without combined pharmacological interventions) for depression following TBI in adults and children are superior to:
  - i) no intervention;
  - ii) pharmacological intervention alone.
2. To compare the effectiveness of different types of non-pharmacological interventions for depression following TBI in adults and children.
3. To investigate the occurrence of adverse effects as a consequence of non-pharmacological interventions in order to assist practitioners in identifying appropriate interventions.
4. To describe how interventions were adapted and modified to suit this population.

## METHODS

### Criteria for considering studies for this review



### Types of studies

This review was restricted to randomised controlled trials (RCTs).

### Types of participants

We included studies of adults or children (or both) who had a TBI and were diagnosed with a depressive condition, or had clinically significant depressive symptoms.

For the purposes of this review, we searched for studies of participants with a history of TBI who had brain damage due to external forces, such as direct impact, either rapid acceleration or deceleration, a penetrating injury, or blast waves from an explosion. We included studies with mixed samples of participants (such as people with non-traumatically acquired brain injuries) if there were data available which allowed separate analysis of participants with TBI.

For the purposes of this review, we searched for studies of participants with depression who either:

- fulfilled the diagnostic criteria for an applicable mood disorder as stated by a well-established diagnostic system such as the DSM-IV-TR (APA 2000), or the International Classification of Diseases (ICD-10; WHO 1992). The applicable diagnoses were major depressive episode, major depressive disorder, dysthymic disorder, mood disorder due to a general medical condition with depressive features, or adjustment disorder with depressed mood; or
- presented with clinically significant depressive symptoms as indicated by subjective report (self- or other-rated) or by observational methods, using standardised measures.

We included studies with participants who had co-morbid psychological conditions, such as anxiety disorders or substance abuse disorders, but we excluded studies with participants with bipolar disorders.

### Types of interventions

We included any form of intervention which was non-pharmacological, which aimed to reduce depressive symptoms or resolve the presence of a diagnosable depressive disorder. Interventions might have been psychological, physical or medical (e.g. electro-convulsive therapy). We had planned to compare the types of interventions against each other, against no intervention, or against other control interventions, such as placebo, usual care, or a control group receiving comparable attention to the intervention group. There were no restrictions on duration or frequency of intervention. We included studies that focused on the presence of depressive disorders or the symptoms of depression. We included studies where participants were concurrently prescribed medications that may have affected depressive symptoms, such as antidepressants or stimulants, provided that medication was not the sole intervention.

### Types of outcome measures

#### Primary outcomes

Our primary outcome was:

- the presence or remission of depressive disorders, as determined by the use of accepted diagnostic criteria (e.g. DSM-IV or ICD-10), by the use of a standardised structured interview based on such criteria (e.g. Structured Clinical Interview for the DSM Disorders), or the results of validated self- or observer-rated questionnaires of depressive symptoms.

#### Secondary outcomes

Where information was available, secondary outcome measures included:

- neuropsychological functioning, psychosocial adjustment, everyday functioning, quality of life, and participation;
- medication usage, healthcare service usage;
- treatment compliance, as indicated by the proportion of withdrawals from intervention;
- the occurrence of suicide or self harm; or
- any adverse effects of the intervention.

The information size required to reliably detect a treatment effect was calculated using a power analysis for a single RCT. The analysis was based on the assumption the RCT would report a continuous outcome; the measure chosen as a representative outcome measure was the Hamilton Scale for Depression (HAM-D; Hamilton 1960). A four-point change on the HAM-D was regarded as clinically significant. We calculated the sample size for a single RCT with 90% power at the 5% significance level as 38 people per group, or 76 in total for a treatment versus control RCT.

### Search methods for identification of studies

In order to reduce publication and retrieval bias we did not restrict our search by language, date, or publication status.

#### Electronic searches

The Cochrane Injuries Group Trials Search Co-ordinator searched the following:

1. Cochrane Injuries Group Specialised Register (February 2015);
2. Cochrane Central Register of Controlled Trials (CENTRAL; *The Cochrane Library* 2015, issue 1);
3. Database of Abstract of Reviews of Effects (DARE; *The Cochrane Library* 2015, issue 1);
4. MEDLINE (OvidSP; 1946 to February 2015);
5. Embase (OvidSP; 1974 to February 2015);
6. CINAHL Plus (EBSCO; 1937 to February 2015);
7. PsycINFO (OvidSP; 1806 to February 2015);

8. PsycBITE (OvidSP; 1806 to May 2012). Search strategies are listed in [Appendix 1](#).

### Searching other resources

The authors searched the following online trials registers to February 2015:

- Current controlled trials ([www.controlled-trials.com](http://www.controlled-trials.com));
- Clinicaltrials.gov ([www.clinicaltrials.gov](http://www.clinicaltrials.gov));
- Trials Central ([www.trialscentral.org](http://www.trialscentral.org)).

We checked reference lists of included studies and previously published reviews for additional material. We also contacted authors and experts in the field to identify additional studies.

We handsearched the following journals and conference proceedings: *Brain Injury* (1992 to February 2015); *Brain Impairment* (2000 to February 2015); *Archives of Physical Medicine and Rehabilitation* (1992 to February 2015); *Neuropsychological Rehabilitation* (1992 to February 2015); the *Journal of Affective Disorders* (1992 to February 2015); and the World Federation for Neuro-Rehabilitation Congress proceedings (2000 to February 2015).

### Data collection and analysis

We collated the search results using EndNote bibliographic software and removed duplicates before two review authors began the screening process.

### Selection of studies

Two review authors (PG and RT) independently inspected all citations identified by the search. They assessed the titles and abstracts to determine whether each article met the predetermined criteria. Where there was inadequate information contained in the abstract and title, they inspected the full article.

They obtained and independently assessed the identified articles to determine whether they met the review criteria. Inter-rater reliability for the study selection was kappa = 0.93 (percent agreement = 99.6%), which reflects 'excellent' agreement ([Higgins 2011](#)). On studies where there was disagreement, they held discussions to reach a consensus. They tracked identified studies using an electronic reference management system (EndNote).

When we found articles in languages other than English, we arranged translation of the paper to assess the eligibility, rate the quality, and extract the data for the trial (where necessary).

### Data extraction and management

We used a specific data extraction form for this review. Two review authors independently extracted data from identified trials and compared the results. When there was doubt or disagreement, they held discussions to reach a consensus. Where there was information missing from a trial, we contacted the original investigators.

### Assessment of risk of bias in included studies

Two authors (PG and RT) independently assessed the studies for methodological quality using the Cochrane 'Risk of bias' tool, which examines bias in studies using the following criteria ([Higgins 2011](#)).

1. Random sequence generation: was the method used to generate allocation adequate to ensure randomisation?
2. Allocation concealment: was allocation to groups adequately concealed in order to prevent prediction of allocation?
3. Blinding of participants and personnel: were the participants and personnel delivering the intervention aware of the intervention group to which participants were allocated?
4. Blinding of outcome assessment: were outcome assessors aware of the group to which the participants had been allocated?
5. Incomplete outcome data: were sufficient data available to draw reliable and meaningful conclusions?
6. Selective reporting: were the reports of the study free of bias in the way in which results were reported?
7. Other sources of bias: were there any other apparent sources of bias?

For each study selected, they provided detailed text and graphic description of the risk of bias, and provided an interpretation based on available information on whether the study was of low, high or unclear risk of bias for each criterion. Where there was disagreement in judgements of bias, they discussed this and reached a consensus. Where information was unavailable to make a judgement, we contacted the study authors and sought further information.

### Measures of treatment effect

#### Continuous data

In studies where the outcome measures related to the severity of depressive symptoms, we expected that these would be continuous outcomes. We calculated the standardised mean difference (SMD) and the 95% confidence interval (CI) for continuous data where comparable measurement scales were used (e.g. Beck Depression Inventory, Hospital Anxiety and Depression Scale, etc.).

#### Dichotomous data

In studies where the outcome measures related to the participants' diagnostic status, we expected dichotomous outcomes. We had planned to analyse these outcomes by calculating the risk ratio (RR), which allows for easier communication of treatment effect and is more consistent across clinical populations than other measures of treatment effect.

### Unit of analysis issues

We found substantial heterogeneity in the nature of the studies included. The possibilities we anticipated were: multiple intervention groups, the use of alternative designs, such as cross-over studies, repeated observation of participants in the case of long-term follow-up, and variability in the dependent measures used.

### Multiple intervention groups

We had planned to combine groups to allow pair-wise comparison of groups, as recommended by [Higgins 2011](#). If this was not possible, we had planned to select one pair of interventions that were comparable with other selected studies and exclude other interventions.

### Cross-over studies

Cross-over studies can be confounded by carry-over effects in the group receiving the intervention first. In studies where this was apparent, we only included data from the first intervention period. If the results from the experimental and control interventions approximated those of parallel studies, we had planned to analyse the data as if they were pair-wise comparisons. While this method of analysis is not ideal, [Higgins 2011](#) indicates that this is likely to lead to a lower weighting of these studies in meta-analysis, due to wider confidence intervals.

### Dealing with missing data

Where possible, we attempted to identify where data were missing and ascertain the missing values. We searched for registered protocols of selected studies and then contacted the original investigators to determine whether all data had been published.

### Assessment of heterogeneity

It was anticipated that there would be heterogeneity due to differences in participant characteristics, clinical outcome measures, or the range of interventions for depression, including psychological, physical and non-pharmacological medical interventions, as well as sub-types within these categories. We assessed the selected trials for the type of intervention used, and grouped trials accordingly. We had planned to assess heterogeneity using the visual inspection method and the  $I^2$  statistic. According to section 9.5.2 of the *Cochrane Handbook of Systematic Reviews of Interventions*, the  $I^2$  statistic can be classified as representing either moderate (30% to 60%), substantial (50% to 90%) or considerable (75% to 100%) heterogeneity ([Higgins 2011](#)). For the purpose of this review, we did not pool the data if the  $I^2$  statistic was greater than 75%.

### Assessment of reporting biases

There was a risk of reporting bias because not all studies would necessarily be published in sources that were easily identifiable ([Higgins 2011](#)). By searching a broad range of sources, including

multiple databases, trials registries, and grey literature, the authors attempted to reduce this risk. When we identified registered trials that had not yet been published, we contacted the investigators to seek further information and data. If sufficient trials had been identified, we had planned to undertake a funnel plot analysis to predict the likelihood of unpublished studies, and the impact this could have on the findings of meta-analyses.

### Data synthesis

If multiple trials were identified that were clinically homogenous (for example, all psychological interventions), in which outcomes had been measured in similar ways, and for which data were available, we had planned to perform meta-analyses using the inverse-variance method. The inverse-variance method can be applied to either dichotomous or continuous data.

### Subgroup analysis and investigation of heterogeneity

If there had been a sufficient number of studies available, we had planned to perform the following subgroup analyses:

- injury severity (mild versus moderate-to-severe TBI);
- age group;
- time post-injury (acute versus long-term);
- categories of intervention (for example, psychological versus physical or medical) and sub-types of interventions (for example, behavioural therapy versus psychodynamic therapy); and
- baseline severity of depression.

We had planned to apply a random-effects model, because it was expected that the included studies would use a variety of intervention delivery methods, which were expected to have variable treatment effects.

### Sensitivity analysis

We had expected that the included studies would vary in their methodological quality and risks of bias. If there had been sufficient studies, we had planned to repeat the meta-analyses, excluding studies which had a high or unclear risk of bias for allocation concealment.

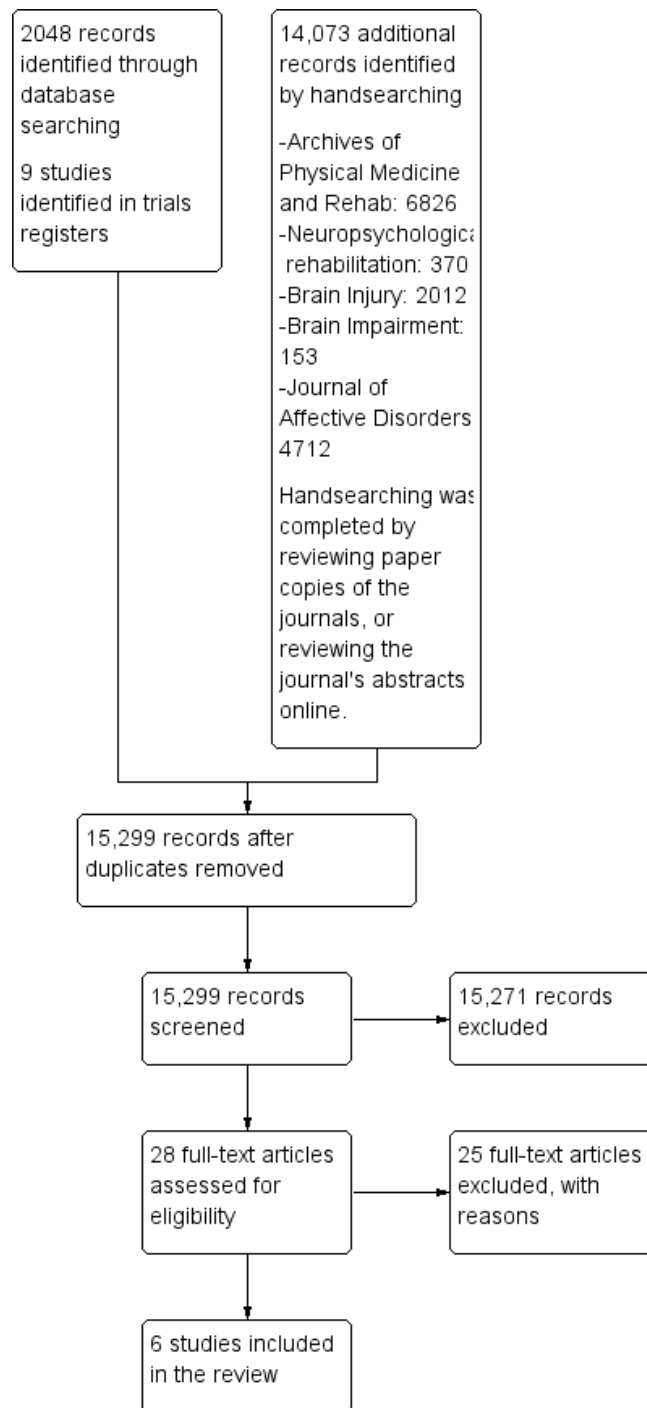
## RESULTS

### Description of studies

#### Results of the search

The most recent search was run on 11 February 2015; the search process is displayed in [Figure 1](#). Two authors (PG and RT) individually searched the titles and abstracts of all of these records and

identified 28 articles that warranted further investigation. Twenty-five of these were excluded, leaving three studies that were eligible for inclusion in the review. In addition, one author (PG) conducted a handsearch of five specified journals and proceedings of one conference (the conference proceedings for another could not be located). The handsearch involved review of the titles of 14,073 articles and further investigation of the abstracts where the title appeared relevant. Aside from studies already identified in the database search, the handsearch did not identify any further studies for investigation.

**Figure 1. Study flow diagram.**

One author (PG) also conducted a search of trials registry databases, which yielded six studies for further investigation. Of these, three were excluded and three RCTs fulfilled the inclusion criteria (Ashman 2014; Bedard 2013; Fann 2015). In addition, four relevant studies are in progress, and are described in the table of [Ongoing studies](#).

### Included studies

The included studies examined the following comparisons:

1. Cognitive behavioural therapy (CBT), or a variant of CBT, versus a waiting list control (Bedard 2013; Fann 2014; Simpson 2011)
2. CBT versus supportive psychotherapy (SPT; Ashman 2014)
3. Repetitive transcranial magnetic stimulation (rTMS) combined with oral tricyclic anti-depressant (TCA) medication versus oral TCA alone (He 2004)
4. Supervised exercise program versus exercise as usual (Hoffman 2010)

Of the six studies that were included, one was conducted in China (He 2004), three in the USA (Ashman 2014; Fann 2015; Hoffman 2010), one in Canada (Bedard 2013), and one in Australia (Simpson 2011). All of the included studies investigated intervention effects in adults. None of the included studies related to people under the age of 18 years.

#### Ashman 2014

This study compared two popular modes of psychological therapy: CBT and supportive psychotherapy (SPT). Participants engaged in up to 16 therapy sessions on a twice-weekly or weekly basis over a three-month period. Seventy-seven participants were allocated to treatment and 43 participants completed the study. Participants who dropped out before the intervention tended to have lower educational attainment and lower income. At baseline, all participants met the inclusion criteria for depression, either by diagnosis or clinical cutoff on a self-report measure (BDI-II score of 20 or higher). All participants had a confirmed history of TBI. The mean age was 47 for both groups, with an average time since injury of 7.8 years for the CBT group and 13.2 for the SPT group. There were more women than men in both groups (CBT group 64% female and SPT group 54% female). The primary outcome measure was diagnosis of depression as measured by the Structured Clinical Interview for the DSM-IV (SCID). There are some missing data for some outcomes and so the number of included participants is different for each outcome measure.

#### Bedard 2013

This study examined the benefit of mindfulness-based cognitive therapy (MBCT) in comparison with wait-list control. All participants met the criteria for depressive symptoms (BDI-II score of 16 or higher) and were engaged in a multi-centre trial of weekly group therapy over a 10-week period. All participants had a his-

tory of TBI. One hundred and five participants were allocated to an intervention. While assignment was randomised, there were five participants who were allocated to the intervention in order to increase participation at one of the treatment centres. Of the 105 participants randomised, 76 completed the study. The MBCT intervention group had an average age of 47.1 and was 50% female, while the average age of the wait-list control group was 46.8 and was 40% female. The primary outcome measure was the Beck Depression Inventory (BDI-II). There are some missing data for some outcomes and so the number of included participants is different for each outcome measure.

#### Fann 2015

This study compared CBT delivered either in person, by telephone, or usual care. Participants were recruited at multiple sites and were included if they had a documented history of TBI, a confirmed diagnosis of major depressive disorder (MDD) on the SCID, and symptom severity was above the clinical cutoff on the Patient Health Questionnaire (PHQ-9). Choice-stratification randomisation gave participants two sets of options to which they could be randomly allocated: the in-person intervention (CBT-IP) or usual care, or the telephone intervention (CBT-T) or usual care. In this way, the authors were able to ensure random allocation and also provide a treatment intervention that suited each participant. One hundred participants were allocated to either CBT-IP (N = 18), CBT-T (N = 40), or usual care (UC, N = 42). The CBT intervention was based on a protocol specifically designed for delivery by telephone over eight weeks. This program was expanded to 12 weeks and adapted for the TBI population by presenting material in smaller portions, more slowly and with greater repetition. In many instances, support people were involved in the treatment sessions. The mean age was 45.4 for the CBT groups and 46.3 for UC. Forty-one percent of the CBT groups and 31% of the usual care groups were female. Mean number of years since injury was 2.84 for the CBT groups and 2.58 for UC. The primary outcome measures were the clinician-administered Hamilton Depression scale (HAM-D; Hamilton 1960), and the self-administered Symptom Checklist-20 (SCL-20).

#### He 2004

This study examined the effect of a non-pharmacological, medical intervention (rTMS) in addition to a pharmacological intervention (TCA). Study participants had a TBI that was confirmed through CT or MRI scans and were included in the study when their score on the HAM-D was eight or higher. Sixty-four patients from a hospital neurosurgery and rehabilitation department met the inclusion criteria. Thirty-two people (15 female) were allocated to the intervention group (rTMS plus TCA) and 32 people (15 female) were allocated to the control group (TCA alone); one control group participant was lost to follow up. The intervention group underwent rTMS on 10 days over a 12-day period. The

mean (SD) age for the intervention group was 37.2 (9.98) years, and 37.4 (10.6) years for the control group. Primary outcome measures were the HAM-D, the Mini-Mental State Examination (MMSE), and plasma monoamine neurotransmitter concentrations, specifically 5-hydroxytryptamine (5-HT) and noradrenaline (NA).

#### Hoffman 2010

This study examined the benefit of a supervised exercise program to improve mood following TBI. Participants were recruited from the practices of medical and allied health professionals, and the local media. In order to be included, participants must have had a history of TBI of at least six months, and not more than five years prior to enrolment, and scored five or more on the Patient Health Questionnaire-9 (PHQ-9). This study excluded people with active suicidal ideation.

Over a 10-week period, the intervention group underwent a weekly exercise session with a personal trainer plus a home-based exercise program that participants were encouraged to complete four times a week. The control group was instructed to exercise as normal and were followed up at the conclusion of 10 weeks. Forty people were allocated to the intervention (25 female) and 40 were allocated to the control intervention (20 female), with 39 completing the intervention and 37 completing the control interventions. The mean age of the intervention group was 39.7 years; the mean age of the control group was 37.1. The primary outcome measure was the score on the Beck Depression Inventory (BDI-II).

#### Simpson 2011

This study examined an intervention specifically for suicide prevention. After consultation with the primary author, it was determined that the study sample consisted of people with depression following TBI, who had presented with the symptom of suicidal ideation or a history of suicide attempts. The study included patients recruited from a hospital-based brain injury community outreach program with TBI, who scored in the moderate or severe range on the Beck Hopelessness Scale (BHS), presented with suicidal ideation, or both. As such, the study met the inclusion criteria by specifying a cutoff on a clinical measure of depression. Subjects were randomised to either an active intervention (N = 8; male/female ratio unknown), or a wait-list control group (N = 9). The intervention was 10 weekly two-hour CBT groups for the treatment of hopelessness, and was structured according to a

treatment manual entitled 'Window to Hope'. The mean (SD) age of participants was 39.4 (12.4) years for the intervention group and 44.1 (11.7) years for the control group. The mean time (SD) post-injury was 6.3 (6.8) years for the intervention group and 7.6 (4.6) years for the control group. The median duration of post-traumatic amnesia (PTA) was 10 days for the intervention group and 21 days for the control group.

The primary outcome measure was the Beck Hopelessness Scale (BHS). Secondary outcomes measures were the Beck Scale for Suicidal Ideation (BSS), the Hospital Anxiety and Depression Scale (HADS), the Herth Hope Index, the Rosenberg Self-Esteem Scale and the Social Problem-Solving Inventory-Revised (SPSI-R).

### Excluded studies

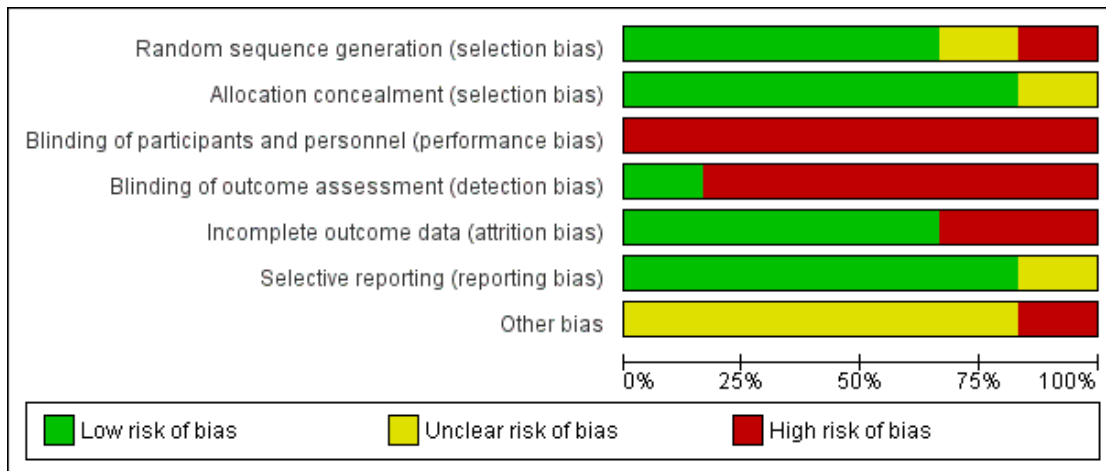
Twenty-five studies were identified but excluded for at least one of the following reasons: the inclusion criteria did not specify either a diagnosis of depression or a clinical cutoff on a depression scale (21 studies); the intervention was not for depression (12 studies); the sample included people with non-traumatic brain injuries, participants with TBI could not be clearly identified from the published article and it was not feasible to contact the authors about extracting individual data for people with TBI because the studies were conducted a long time ago (six studies); the intervention was found to be pharmacological (one study); and the study was not a RCT (one study).

Most excluded studies reported intervention outcomes for adults; two studies reported treatment outcomes for children (Wade 2006), or adolescents (Wade 2008).

### Risk of bias in included studies

The included studies were assessed using the Cochrane 'Risk of Bias' tool, according to chapter 8 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). Data were extracted from the included studies in order to classify low, high or unclear risk for the following criteria; allocation sequence was randomised, allocation to groups was concealed, blinding of participants and personnel, blinding of outcome assessment, attrition of participants to final outcome collection, selective reporting of outcomes and other potential biases. A summary of the risk of bias is described in Figure 2 and Figure 3.

**Figure 2. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies. Six studies are included in this review.**





**Figure 3. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.**

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias
Ashman 2014	+	+	-	+	-	+	?
Bedard 2013	-	+	-	-	-	+	?
Fann 2015	+	+	-	-	+	+	?
He 2004	?	?	-	-	+	?	?
Hoffman 2010	+	+	-	-	+	+	?
Simpson 2011	+	+	-	-	+	+	-

### Allocation

Selection biases may affect the way in which participants are allocated to groups and may lead to systematic variances in the nature of the participant groups. Selection biases relate to the sequence in which participants were allocated to groups (*sequence generation*) and also the awareness of the group that participants may be allocated to (*allocation concealment*). Some studies are not truly random because they may employ a non-random selection sequence (such as, allocation by month of birth) which introduces the possibility of bias in the study findings. Where participants or personnel might be aware of the allocation sequence this might influence participants' inclusion in the study.

In [He 2004](#), the risk of bias for random allocation was unclear. The allocation sequence was determined before allocation to groups, however there is insufficient detail to determine how the allocation sequence was determined and whether a truly random sequence was generated. In [Ashman 2014](#), [Simpson 2011](#) and [Hoffman 2010](#) there was low risk of selection bias as the authors employed a computer generated sequence determined prior to allocation. [Fann 2015](#) employed choice-stratified randomisation, which was assessed as low risk of bias.

For [Bedard 2013](#), randomisation was conducted by a statistician who was independent of the clinicians and site investigators. The statistician used a minimisation procedure to ensure balance at baseline between the groups on a key outcome measure (BDI-II). These measures point to a low risk of selection bias. However, five participants at one site were allocated to the intervention intervention because there were low participant numbers at that site rather than being randomly allocated to intervention; therefore, the study was reclassified at a high risk of bias on this criterion.

### Blinding

Blinding refers to the processes that the study authors implemented in order to prevent participants finding out to which intervention they had been allocated (*performance bias*) and to prevent personnel conducting outcome assessments from detecting to which intervention participants had been allocated (*detection bias*).

Five studies demonstrated high risk of performance bias ([Bedard 2013](#); [Fann 2015](#); [He 2004](#); [Hoffman 2010](#); [Simpson 2011](#)). This was because in each study the intervention was compared with a control that involved little or no intervention. In these studies, the intervention required subjects to attend for a specific treatment, whereas control participants were instructed to continue on with their lives as usual.

In [Ashman 2014](#), there was less risk of performance bias since participants from each intervention received a similar level of clinician attention. However, it was not possible for the personnel pro-

viding the intervention to be blind to the intervention, and there is also the risk that if participants from each intervention were to compare their treatment they would find them to be distinct, therefore this was also assessed as high risk of bias.

Only one study demonstrated low risk of detection bias, since the primary outcome measure was a diagnostic assessment conducted by an independent clinician ([Ashman 2014](#)). In four other studies ([Fann 2015](#); [He 2004](#); [Hoffman 2010](#); [Simpson 2011](#)), there was an attempt to minimise detection bias by using different personnel to conduct the outcome assessments. In [Simpson 2011](#), participants were requested not to disclose their group allocation to the outcome assessor. Nevertheless, all studies except [Ashman 2014](#) relied upon primary outcome measures which were either self-report scales or had a heavy component of self-report (such as the HAM-D in [Fann 2015](#)) and as such must be considered at high risk of bias.

### Incomplete outcome data

Attrition bias refers to the potential confounding influence of substantial dropout from the study. Often this is because of systemic issues within the study, such as a particularly demanding treatment intervention.

Four studies were rated as low risk for attrition bias as there was minimal dropout ([Fann 2015](#); [He 2004](#); [Hoffman 2010](#); [Simpson 2011](#)). For these four studies, of the 261 participants randomised, outcome data were collected on 241 (92%). Two studies were rated as high risk for attrition bias due to substantial dropout ([Ashman 2014](#); [Bedard 2013](#)).

### Selective reporting

Selective reporting refers to bias that can be introduced when the study authors fail to report all the outcomes that they intended to collect. This is more often true of findings that are not statistically significant. In order to be classified as low risk on this criterion there must be an a priori study protocol available ([Higgins 2011](#)). [He 2004](#) was classified as unclear risk due to a lack of information that could identify a priori the outcome measures (e.g. a protocol for the study that pre-dated the publication). The other five studies were classified as low risk. For four studies, there were registered trial protocols available which indicated that the primary outcome measures that were planned were in fact used ([Ashman 2014](#); [Bedard 2013](#); [Fann 2015](#); [Simpson 2011](#)). In the case of [Hoffman 2010](#), personal communication with the authors confirmed that all outcomes were reported in the final publication.

### Other potential sources of bias

A potential source of bias affecting [Simpson 2011](#) is the small sample size of  $N = 17$  (intervention group,  $N = 8$  and control group,  $N = 9$ ). The baseline characteristics of the groups were not significantly different according to statistical tests, however, there was a clinically meaningful difference between the groups relating to the mean duration of post-traumatic amnesia (intervention group, PTA = 10 days and control group, PTA = 21 days), which is a key clinical indicator of the severity of TBI. The authors reported that the data pertaining to PTA and time since injury were not normally distributed between the groups and this could have biased the findings.

## Effects of interventions

See: [Summary of findings for the main comparison CBT compared to wait-list control for post-TBI depression](#); [Summary of findings 2 CBT compared to Supportive Psychotherapy for Post-TBI Depression](#); [Summary of findings 3 Repetitive transcranial magnetic stimulation \(rTMS\) compared to rTMS plus Tricyclic Anti-depressant for Post-TBI Depression](#); [Summary of findings 4 Supervised exercised compared to Exercise as usual for Post-TBI Depression](#)

### Comparison one: cognitive-behavioural therapy (CBT) or variant of CBT versus waiting list<sup>2</sup>

#### 1.1 Depression diagnosis (ITT analysis)

One study (100 participants) compared CBT with waiting list for the outcome depression diagnosis ([Fann 2015](#)). The intention-to-treat (ITT) analysis included 58 CBT participants and 42 controls, with a depression diagnosis of 34% for CBT versus 52% for controls (RR 0.66; 95% CI 0.42 to 1.04;  $Z = 1.79$ ;  $P = 0.07$ ; [Analysis 1.1](#)) at the end of the intervention period. After the eight-week follow-up period, depression diagnosis was 40% for CBT versus 45% for controls (RR 0.88; 95% CI 0.55 to 1.39;  $Z = -0.56$ ;  $P = 0.58$ ; [Analysis 1.2](#)).

#### 1.2 Reduction in depression symptoms

Three studies (146 participants) compared CBT, or a variant of CBT, with a no-treatment control and were combined in a meta-analysis in which the most commonly used depression measure was chosen as the outcome (BDI-II, HAM-D and HADS depression scales; [Bedard 2013](#); [Fann 2015](#); [Simpson 2011](#)). The  $I^2$  statistic was applied and demonstrated minimal statistical heterogeneity ( $I^2 = 0\%$ ;  $\text{Chi}^2 = 1.56$ ;  $\text{df} = 2$ ;  $P = 0.46$ ), which confirmed the appropriateness of performing a meta-analysis ([Analysis 1.3](#)). The standardised mean difference (SMD) was  $-0.14$  (95% CI  $-0.47$  to  $0.19$ ;  $Z = 0.83$ ;  $P = 0.41$ ), indicating no difference was attributable to the intervention when outcomes were measured at the end of the interventions. The quality of the evidence was very-low,

indicating that we are uncertain this estimate represents a true treatment effect. The studies also reported long-term follow-up data, collected at either two or three months after completion of the intervention; the SMD was  $-0.02$  (95% CI  $-0.33$  to  $0.29$ ;  $Z = 0.12$ ;  $P = 0.91$ ; [Analysis 1.4](#)), indicating no effect of treatment.

#### 1.3 Secondary outcomes

All studies that compared CBT or a variant of CBT with a waiting list assessed outcomes with additional depression measures. Two studies used a version of the Symptom Checklist (SCL) as a secondary measure of depression symptoms; these studies were combined for meta-analysis ([Bedard 2013](#); [Fann 2015](#);  $N = 175$ ). There was minimal heterogeneity ( $I^2 = 0\%$ ;  $\text{Chi}^2 = 0.01$ ;  $\text{df} = 1$ ;  $P = 0.90$ ), with no difference between CBT and waiting list groups. The SMD was  $-0.15$  (95% CI  $-0.45$  to  $0.15$ ;  $Z = 1.0$ ;  $P = 0.32$ ; [Analysis 1.5](#)). In a separate analysis, [Fann 2015](#) found that participants who completed at least eight of 12 CBT sessions had improved SCL-20 scores when compared with the control group at the end of treatment (treatment effect  $0.43$ ; 95% CI  $0.10$  to  $0.76$ ;  $P = 0.011$ ). This study conducted follow-up eight weeks after the completion of the intervention, and found that the benefit did not continue (no effect on the SCL-20; SMD  $0.01$ ; 95% CI  $-0.38$  to  $0.41$ ;  $Z = 0.06$ ;  $P = 0.95$ ; [Analysis 1.6](#)).

[Fann 2015](#) also analysed outcomes for secondary measures of depression. These included the inventories of symptom improvement, as measured by the Patient Global Impression (PGI), and satisfaction with depression care. There was a difference on the PGI, with more participants in the CBT group rating their depression symptoms as 'much or very improved' (RR  $0.67$ ; 95% CI  $0.47$  to  $0.96$ ;  $Z = 2.18$ ;  $P = 0.03$ ; [Analysis 1.7](#)), but this was not maintained at long-term follow-up (RR  $0.75$ ; 95% CI  $0.54$  to  $1.05$ ;  $Z = 1.68$ ;  $P = 0.09$ ; [Analysis 1.8](#)). Similarly, at the end of treatment, there was a statistically significant difference on a Likert rating scale of satisfaction, with CBT participants three times more likely to report that they were 'moderately or very satisfied' with their depression care than participants assigned to usual care (RR  $0.35$ ; 95% CI  $0.22$  to  $0.55$ ;  $Z = 4.60$ ;  $P < 0.0001$ ; [Analysis 1.9](#)).

[Bedard 2013](#) used the Patient Health Questionnaire (PHQ-9) as a secondary measure of depression. There was no difference on outcome between participants receiving Mindfulness-based CBT and those on the waiting list (SMD  $-0.41$ ; 95% CI  $-0.87$  to  $0.05$ ;  $Z = 1.76$ ;  $P = 0.08$ ; [Analysis 1.10](#)).

[Simpson 2011](#) measured hopelessness, suicidality and self-esteem at the end of treatment. There was a difference of one point on the Beck Hopelessness Scale (BHS), SMD  $-1.04$  (95% CI  $-2.07$  to  $-0.01$ ;  $Z = 1.98$ ;  $P = 0.05$ ; [Analysis 1.11](#)). There was no difference between treatment groups on the Beck Scale for Suicidal Ideation (BSS), SMD  $-0.49$  (95% CI  $-1.46$  to  $0.48$ ;  $Z = 0.98$ ;  $P = 0.33$ ; [Analysis 1.12](#)). There was no difference between treatment groups on the Rosenberg Self-Esteem Scale (SMD  $0.00$ ; 95% CI  $-0.95$

to 0.95;  $Z = 0.00$ ;  $P = 1.0$ ; [Analysis 1.13](#)).

#### 1.4 Treatment compliance, withdrawals from study (dropouts)

One hundred and twenty-three people were allocated to a CBT or variant intervention and 98 completed the study (79%). Ninety-nine people were allocated to a waiting-list control group and 83 completed outcome measures (84%). This was subjected to an ITT analysis which demonstrated low heterogeneity ( $I^2 = 35\%$ ;  $\text{Chi}^2 = 1.55$ ;  $\text{df} = 1$ ;  $P = 0.21$ ). There was no difference in withdrawals from the study between the CBT and waiting list groups (RR 1.20; 95% CI 0.57 to 2.54;  $Z = 0.49$ ;  $P = 0.63$ ; [Analysis 1.14](#)).

#### 1.5 Any adverse effects

No adverse effects were reported.

### Comparison two: CBT versus Supportive Psychotherapy (SPT)

The only study of this comparison was [Ashman 2014](#).

#### 2.1 Depression diagnosis (ITT analysis)

[Ashman 2014](#) found that following the intervention, 64% of the CBT group and 84% of the SPT group still had a diagnosis of major depressive disorder; the difference in remission was not statistically significant (RR 0.76; 95% CI 0.58 to 1.00;  $Z = 1.96$ ;  $P = 0.05$ ; [Analysis 2.1](#)).

#### 2.2 Reduction in depression symptoms

There was no difference between treatment groups in BDI-II score (SMD -0.09; 95% CI -0.65 to 0.48;  $Z = 0.30$ ;  $P = 0.77$ ; [Analysis 2.2](#)). The combined-groups sample demonstrated a modest mean reduction in BDI-II score regardless of group allocation ( $F(1, 47) = 9.63$ ,  $p = 0.003$ ). The quality of the evidence was very-low, indicating that we are uncertain this estimate represents the true treatment effect.

#### 2.3 Secondary outcomes

There was no difference in the Life 3 Quality of Life inventory between participants who received CBT or SPT (SMD -0.06; 95% CI -0.52 to 0.39;  $Z = 0.27$ ;  $P = 0.78$ ; [Analysis 2.3](#)).

#### 2.4 Treatment compliance, withdrawals from study (dropouts)

Seventy-seven participants were allocated to treatment by [Ashman 2014](#) but only 43 participants completed a treatment. There was no difference in treatment completion between CBT and SPT

(RR 0.97; 95% CI 0.59 to 1.61;  $Z = -0.10$ ;  $P = 0.92$ ; [Analysis 2.4](#)).

#### 2.5 Any adverse effects

No adverse effects were reported.

### Comparison three: repetitive transcranial magnetic stimulation (rTMS) plus tricyclic antidepressant (TCA) versus TCA alone

The only study of this comparison was [He 2004](#).

#### 3.1 Remission of depression diagnosis (ITT analysis)

ITT analysis was not reported.

#### 3.2 Reduction in depression symptoms

[He 2004](#) compared the effect of rTMS plus TCA to TCA alone. The main outcome measure was the Hamilton Depression scale (HAM-D). A four-point change on the HAM-D is regarded as clinically significant. There was a clinically irrelevant difference in favour of rTMS plus TCA (SMD -0.84; 95% CI -1.36 to -0.32;  $Z = 3.19$ ;  $P = 0.001$ ; [Analysis 3.1](#)). The quality of the evidence was very-low, indicating that we are uncertain this estimate represents the true treatment effect.

#### 3.3 Secondary outcomes

[He 2004](#) included the Mini Mental State Exam (MMSE) score as a secondary outcome measure and found a statistically significant change in favour of the rTMS plus TCA intervention, but the change was not clinically relevant (SMD -0.99; 95% CI -1.51 to -0.46;  $Z = 3.69$ ;  $P = 0.0002$ ; [Analysis 3.1](#)). A change of at least 1.5 points on the MMSE is considered clinically significant.

[He 2004](#) included serotonin levels as a secondary outcome measure and found no difference between groups (SMD -0.19; 95% CI -0.68 to 0.31;  $Z = 0.75$ ;  $P = 0.45$ ; [Analysis 3.3](#)). Another secondary outcome measure was noradrenaline levels, which were slightly higher in the rTMS plus TCA group (SMD 1.31; 95% CI 0.76 to 1.86;  $Z = 4.69$ ;  $P < 0.0001$ ; [Analysis 3.4](#)).

#### 3.4 Treatment compliance, withdrawals from study (dropouts)

Sixty-four participants were enrolled in [He 2004](#). There were no withdrawals from the intervention group and only one participant withdrew from the control group (RR 0.33; 95% CI 0.01 to 7.89;  $Z = -0.68$ ;  $P = 0.49$ ; [Analysis 3.5](#)).

### 3.5 Adverse effects

Two participants reported transient tinnitus, but this did not affect participation and in each case there was spontaneous remission.

### Comparison four: supervised exercise versus exercise as usual

There was one study of this comparison ([Hoffman 2010](#)).

#### 4.1 Remission of depression diagnosis (ITT analysis)

Diagnostic status was not examined.

#### 4.2 Reduction in depression symptoms

The primary outcome measure in [Hoffman 2010](#) was the Beck Depression Inventory (BDI). There was no difference on the BDI score between groups (SMD -0.43; 95% CI -0.88 to 0.03; Z = 1.84; P = 0.07; [Analysis 4.1](#)). [Hoffman 2010](#) noted that the groups were not equivalent at baseline for the main outcome measure. The quality of the evidence was rated as moderate, and it is likely that further research would have an impact on our confidence in the estimate.

#### 4.3 Secondary measures

[Hoffman 2010](#) collected a variety of secondary outcomes, however did not provide variability data, which precluded independent

analyses. They reported a reduction in pain on the Brief Pain Inventory (P = 0.03) and a reduction in pain interference (P = 0.02). No differences were found for measures of head injury symptoms, perceived quality of life, sleep, general health status, heart rate, or ability to walk. One of the secondary outcomes collected was frequency of exercising. During the 10-week course, participants in the intervention group increased their frequency of exercise from a mean of 1.28 days per week to 3.68, whereas the control participants increased from 1.47 to 2.05 days per week. The duration of exercise increased accordingly: in the intervention group from a mean of 58 minutes to 143 minutes per week; and in the control group from a mean of 66 minutes to 252 minutes per week.

#### 4.4 Treatment compliance, withdrawals from the study (dropouts)

Eighty-four participants were enrolled in the [Hoffman 2010](#) study and 76 completed the outcome assessments. There was no difference in completion of treatment between treatment groups (RR 1.67; 95% CI 0.43 to 6.53; Z = 0.73; P = 0.46; [Analysis 4.2](#)).

#### 4.5 Adverse effects

[Hoffman 2010](#) did not report on adverse effects, but did comment that exercise has relatively few adverse effects compared to pharmacological interventions.

## ADDITIONAL SUMMARY OF FINDINGS *[Explanation]*

CBT compared to Supportive Psychotherapy for Post-TBI Depression						
<b>Patient or population:</b> Post-TBI Depression <b>Settings:</b> Community setting <b>Intervention:</b> CBT <b>Comparison:</b> Supportive Psychotherapy						
Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Supportive Psychotherapy	CBT				
Beck Depression Inventory (BDI); higher score means more depressed	The mean BDI score in the control group was 20.4 <sup>3</sup>	The mean BDI in the intervention group was 0.09 standard deviations lower (0.65 lower to 0.48 higher)	SMD -0.09 (-0.65 to 0.48)	48 (1 RCT)	⊕○○○ VERY LOW <sup>1,2</sup>	
<p>*The basis for the <b>assumed risk</b> (e.g. the median control group risk across studies) is provided in footnotes. The <b>corresponding risk</b> (and its 95% confidence interval) is based on the assumed risk in the comparison group and the <b>relative effect</b> of the intervention (and its 95% CI).</p> <p><b>CI:</b> Confidence interval;</p> <p>GRADE Working Group grades of evidence  <b>High quality:</b> Further research is very unlikely to change our confidence in the estimate of effect.  <b>Moderate quality:</b> Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.  <b>Low quality:</b> Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.  <b>Very low quality:</b> We are very uncertain about the estimate.</p>						

<sup>1</sup>Very high dropout rate (attrition bias). As with other studies in this field, blinding of participants and personnel was not achieved (performance bias).

<sup>2</sup>Very wide 95% confidence interval.

<sup>3</sup>The assumed risk is the mean score of the control group.

Repetitive transcranial magnetic stimulation (rTMS) compared to rTMS plus Tricyclic Anti-depressant for Post-TBI Depression						
<b>Patient or population:</b> Post-TBI Depression <b>Settings:</b> People receiving care through a hospital neurology department (not specified whether in-patient or out-patient) <b>Intervention:</b> Repetitive transcranial magnetic stimulation (rTMS) <b>Comparison:</b> rTMS plus Tricyclic Antidepressant						
Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	rTMS plus Tricyclic Anti-depressant	Repetitive transcranial magnetic stimulation (rTMS)				
Hamilton Rating Scale for Depression (HAM-D); higher score means more depressed	The mean HAM-D score in the control group was 6. <sup>3</sup>	The mean HAM-D in the intervention group was 0.84 standard deviations lower (1.36 lower to 0.32 lower)	SMD -0.84 (-1.36 to -0.32)	63 (1 RCT)	⊕○○○ VERY LOW <sup>1,2</sup>	
*The basis for the <b>assumed risk</b> (e.g. the median control group risk across studies) is provided in footnotes. The <b>corresponding risk</b> (and its 95% confidence interval) is based on the assumed risk in the comparison group and the <b>relative effect</b> of the intervention (and its 95% CI). <b>CI:</b> Confidence interval;						
GRADE Working Group grades of evidence <b>High quality:</b> Further research is very unlikely to change our confidence in the estimate of effect. <b>Moderate quality:</b> Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate. <b>Low quality:</b> Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate. <b>Very low quality:</b> We are very uncertain about the estimate.						

<sup>1</sup>High or unclear risk relating to selection, performance, detection, reporting and other biases.

<sup>2</sup>Very wide 95% confidence interval.

<sup>3</sup>The assumed risk is the mean score of the control group.

Supervised exercised compared to Exercise as usual for Post-TBI Depression						
<b>Patient or population:</b> Post-TBI Depression <b>Settings:</b> Community setting <b>Intervention:</b> Supervised exercises <b>Comparison:</b> Exercise as usual						
Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Exercise as usual	Supervised exercised				
Beck Depression Inventory (BDI); higher score means more depression	The mean BDI score in the control group was 16.4. <sup>3</sup>	The mean BDI in the intervention group was 0.43 standard deviations lower (0.88 lower to 0.03 higher)	SMD -0.43 (-0.88 to 0.03)	77 (1 RCT)	⊕⊕○○ LOW <sup>1,2</sup>	
<p>*The basis for the <b>assumed risk</b> (e.g. the median control group risk across studies) is provided in footnotes. The <b>corresponding risk</b> (and its 95% confidence interval) is based on the assumed risk in the comparison group and the <b>relative effect</b> of the intervention (and its 95% CI).</p> <p><b>CI:</b> Confidence interval;</p> <p>GRADE Working Group grades of evidence  <b>High quality:</b> Further research is very unlikely to change our confidence in the estimate of effect.  <b>Moderate quality:</b> Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.  <b>Low quality:</b> Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.  <b>Very low quality:</b> We are very uncertain about the estimate.</p>						

<sup>1</sup>Study subject to risk of biases consistent with the highest quality studies in this population. High risk of bias relates to lack of blinding of participants and personnel (performance bias) and lack of blinding of outcome assessors (detection bias).

<sup>2</sup>Very wide 95% confidence interval.

<sup>3</sup>The assumed risk is the mean score of the control group.



## DISCUSSION

### Summary of main results

The aim of this review was to investigate the effectiveness of non-pharmacological interventions for depression in adults and children following traumatic brain injury (TBI). Following an exhaustive search process, six studies were identified that met strict criteria for inclusion, including three that were completed recently in 2013 and 2014. We identified no studies that investigated an intervention for children or adolescents, and so it is not possible to comment on the efficacy of any intervention for people under the age of 18.

The primary objective was to determine whether non-pharmacological interventions (either with or without pharmacological interventions) for depression in adults and children following TBI were superior to (a) no intervention or (b) pharmacological intervention alone. Four studies compared an intervention with no intervention or treatment as usual. Three of these investigated a psychological intervention that was either cognitive-behavioural therapy (CBT; [Fann 2015](#); [Simpson 2011](#)), or mindfulness-based cognitive therapy ([Bedard 2013](#)). The quality of evidence in support of psychological interventions was very low due to methodological limitations, small effect sizes and very wide confidence intervals of effect size. One study investigated an exercise intervention ([Hoffman 2010](#)). While there was an effect in favour of the intervention, the experimental groups were not equivalent at baseline and no conclusion could be drawn about the effects of exercise as an intervention for mood. One study investigated a combination of a non-pharmacological intervention (repetitive transcranial magnetic stimulation (rTMS)) and a pharmacological intervention (tricyclic antidepressant (TCA)) compared with a pharmacological intervention (TCA alone; [He 2004](#)). This study did find an effect in favour of the combined intervention, however, the quality of the evidence was judged to be very low.

Prior to 2013, there was a paucity of high quality evidence related to the benefit of psychological interventions for depression following TBI. The results of our meta-analysis did not support the effectiveness of psychological interventions compared with no treatment. The studies showed that many participants improved without intervention, and there was a lack of evidence to indicate the reasons that some individuals responded to treatment but others did not.

[Ashman 2014](#) was the only study that compared two active psychological interventions (CBT versus supportive psychotherapy (SPT)), and did not provide evidence in support of one intervention above the other. In addition, the dropout rate from the psychological intervention was high, suggesting that the treatment as delivered was not practical for a large proportion of people with TBI.

### Overall completeness and applicability of evidence

The second stated objective of the review was to compare the effectiveness of different types of non-pharmacological interventions for depression in adults and children following TBI. The six included studies described five different interventions, three psychological (CBT, mindfulness-based cognitive therapy (MBCT), and SPT) and two physical interventions (rTMS and supervised exercise). Only one of these studies compared two active non-pharmacological interventions and found no difference between CBT and another psychological intervention, SPT ([Ashman 2014](#)). Three of the studies investigating a psychological intervention were published in the two years prior to the completion of this review; prior to that, there was a lack of research on arguably the most commonly applied class of non-pharmacological interventions. With the addition of these three studies, and ongoing research on this topic, we are encouraged that current research activities will clarify the true effects of available treatments.

The third stated objective of the review was to investigate the occurrence of adverse effects as a consequence of non-pharmacological interventions in order to assist practitioners in identifying appropriate interventions. Only one study reported adverse effects, and these were reported as minimal ([He 2004](#)). Two participants reported tinnitus (ringing in the ears) that spontaneously resolved. Repetitive transcranial magnetic stimulation (rTMS) has had proven efficacy in the non-brain injured population, but it has not been investigated in the TBI population because of concern about possible adverse effects, particularly increased risk of seizures ([Fitzgerald 2011](#)). Studies of other interventions did not comment on adverse effects.

The fourth stated objective of the review was to describe how interventions were adapted and modified to suit this population. In the case of two studies, it is not clear if the intervention was adapted or modified specifically for the population of people with TBI ([He 2004](#); [Hoffman 2010](#)). [Ashman 2014](#), [Bedard 2013](#), [Fann 2015](#) and [Simpson 2011](#) used CBT programs that were adapted for people with TBI. Common adaptations included providing additional sessions, reducing and repeating the session content, and providing a workbook that accompanied the treatment sessions in order to aid memory. Other modifications included the addition of Motivational Interviewing and problem-solving for TBI-specific symptoms at the outset of the intervention.

### Quality of the evidence

Each selected study was reviewed for quality using the Cochrane 'Risk of bias' tool. All studies were judged to be at high risk of bias due to a lack of blinding of participants and personnel. This could have introduced bias because some participants were aware that they were receiving an active intervention, while others received no additional treatment. Knowledge that they were receiving an active

intervention may have biased their scores on self-rated outcome questionnaires. This also introduced a high risk of detection bias (blinding of outcome assessment) for all studies that relied on these as the primary outcome measures. The exception was [Ashman 2014](#), which used diagnostic status on an independent, blinded, clinician-rated interview as the primary outcome measure. [Fann 2015](#) also applied this as a secondary outcome.

Given the nature of the interventions, it is not necessarily possible to arrange blinding of participants, however, it is possible to deliver control interventions which appear to the participants to be active treatment. For instance, [He 2004](#) could have created a sham rTMS intervention that involved fitting the equipment onto the control participants' heads, but not turning it on. In another study of CBT, a social contact intervention (a social activity group) served as a control intervention, which appeared to the participants to be active treatment ([McDonald 2008](#)). [Hoffman 2010](#) suggested that a social contact intervention could have been employed as a control intervention for their study of supervised exercise.

Participation was a source of bias for the psychological intervention studies. [Ashman 2014](#) and [Bedard 2013](#) were both affected by substantial dropout (attrition bias). [Fann 2015](#) reported a much lower dropout rate, however it was noted that 43% of patients contacted declined to participate in the study. [Simpson 2011](#) was limited by small sample size, and this may have influenced the equivalence of groups, due to possible heterogeneity of participants.

### Potential biases in the review process

Prior to conducting the review, a preliminary search identified 19 studies of non-pharmacological interventions which used a depression scale as an outcome measure. In most cases, these studies did not specify a diagnosis of depression or a cut-off score on a depression scale, as an inclusion criteria. Many of these studies sought to treat more general concepts, such as 'quality of life' or 'psychological well-being'. In reviewing these studies, it was clear that they had failed to adequately address the question of whether the treatment had been effective for depression, because the researchers did not study a sample of participants who were depressed. Therefore, the authors of this review made the decision to exclude studies where a diagnosis of depression, or score on a depression measure, was not specified as an inclusion criterion. In doing so, this introduced a potential source of bias, because it restricted the studies that could be included, some of which were of clinical interest. Alternatively, the authors of this review felt that studies that had depression diagnosis or symptoms as an inclusion criterion were more likely to show a treatment effect, and were more clinically relevant, because they more closely represented patients seen in clinical practice.

There were several studies identified for possible inclusion that had mixed samples that included people with diagnoses other than TBI. In these studies, it was likely that many of the participants had TBI and would have met the inclusion criteria for depression,

however, because it was not possible to identify separate outcome data for these particular individuals, the studies could not be considered (e.g. [Teasdale 1995](#)). Similarly, studies that did not purport to treat depression specifically were excluded, therefore, some interventions devised for other clinical problems, which may be of benefit for depression, were not able to be considered in this review.

At the protocol stage, the sources of studies were specified. At this stage, key decisions were made about which sources to search, and it is possible that key sources were missed. In relation to the electronic database search, the sources were recommended by the Cochrane Injuries Group, and the search strategy was developed by the Trials Search Co-ordinator. The authors of this review specified additional sources to search. It is unlikely that key sources for research on TBI were missed because the literature on this topic tends to be published in key journals. However, in the case of depression, the sources for literature on affective disorders are published more widely, and it is more likely that if studies were missed, it would be in this literature.

The review authors set out to identify key conferences that would represent research in both TBI and depression. Although it was possible to search the proceedings of international conferences relating to TBI (Special Interest Group in Neuropsychological Rehabilitation of the World Federation for Neuro-Rehabilitation, 2000 to present and the International Brain Injury Association (IBIA), 1992 to present), the proceedings of the World Congress of Behavioural and Cognitive Therapies (1993 to present) were unavailable because they were not published in a central journal and the authors could not locate paper copies of the proceedings through personal contacts. Therefore an identified source of studies was not searched.

### Agreements and disagreements with other studies or reviews

There have been several other review papers that relate to treatment of depression following TBI. These include literature reviews and clinician guidelines for the treatment of depression following TBI (e.g. [Alderfer 2005](#)), or mild TBI ([Silver 2009](#)), and a literature review examining the efficacy of CBT as a treatment for depression following TBI and other acquired brain impairments ([Khan-Bourne 2003](#)). There were some systematic reviews that had a similar objective to this review ([Fann 2009](#); [Guillamondegui 2011](#); [Rapoport 2012](#); [Rosenthal 1998](#); [Waldron 2013](#)), two reviews that were limited to depression following mild TBI ([Bay 2009](#); [Barker-Collo 2013](#)), and another that reviewed psychological interventions across a range of interventions affecting people with mild TBI ([Snell 2009](#)). These systematic reviews are discussed in chronological order.

#### [Rosenthal 1998](#)

At the time of publication of this review, the authors found no RCTs of any type of intervention for depression following TBI.

This is consistent with the current review, in which all of the identified studies were published from 2004 onwards.

#### Fann 2009

This review engaged in a widespread search of databases, similar to a Cochrane review. It was far more inclusive than the current review, and included any peer-reviewed study of pharmacological and non-pharmacological interventions, where depression or depressive symptoms were primary or secondary outcomes. As such, it was not restricted to RCTs and as a consequence, it included a greater number of studies. Of the 16 studies included, six were non-pharmacological physical interventions, and 10 were psychotherapeutically-based interventions. It did not include the studies included in the current review since most were published following its publication (Ashman 2014; Bedard 2013; Fann 2015; Hoffman 2010; Simpson 2011), and one was not written in English (He 2004). Fann 2009 noted that none of the studies identified in their systematic review used diagnosis of depression as an inclusion criterion, and of the eight studies of psychological interventions, none specifically set out to treat depression.

#### Guillamondegui 2011

This review was conducted by the Vanderbilt Evidence-based Practice Center, USA and systematically reviewed literature pertaining to TBI and depression including epidemiology, assessment and diagnosis, the course of the condition, and intervention options. This review employed strict selection criteria, which included limiting searches to studies with 50 participants or more. As a consequence, Guillamondegui 2011 identified only two studies of pharmacological interventions, and none of non-pharmacological interventions. The search included studies from 1966 up to May 2010 and was also limited to English-language articles, therefore missing the studies identified in the current review. The authors concluded that no evidence was available to guide treatment choices after TBI.

Rapoport 2012 sought to provide an 'up-to-date selective review' of the current epidemiology, risk factors, and management strategies of major depression following TBI. The search was limited to articles published from 2006 to 2011 that were available on the MEDLINE database. The review included studies that were not RCTs, and studies of mixed acquired brain injury, not just TBI samples. Rapoport 2012 found three studies investigating physical exercise interventions (including Hoffman 2010 identified in the current review), and three pertaining to CBT. Rapoport 2012 concluded that the evidence regarding interventions was inconclusive, and although CBT and exercise interventions showed promise, those studies were subject to bias due to the inclusion criteria not specifying either a diagnosis of depression or the existence of clinically significant depressive symptoms. The advice to clinicians was to follow best practice guidelines for treating major depression in the general population.

Waldron 2013 reviewed outcomes for CBT interventions for anxiety and depression following acquired brain injury (including non-traumatic injuries such as cerebrovascular events, hypoxic or

neurotoxic injuries). The review authors did not limit the search to RCTs. Describing their study selection criteria as 'relaxed', the authors sought to assemble a broad spread of research data that related to the efficacy of CBT. Therefore, Waldron 2013 includes 24 studies of various designs, including 12 studies of single-case designs, two of uncontrolled group studies and 10 RCTs of varying quality. They applied the PEDro methodological rating scale to the studies and found that the quality of the studies ranged from very low (2/10) to acceptable (7/10), with the acknowledgement that it is difficult to achieve several items on the PEDro scale, such as blinding of participants and therapists, due to the nature of the studies. Seven of 24 included studies identified mood as an outcome. Waldron 2013 combined many of these studies in a meta-analysis, despite the variety of clinical problems targeted and interventions applied, concluding that CBT had demonstrated efficacy for the clinical problem it sought to address (e.g. anger management), but these effects did not generalise to other clinical problems such as depression, unless that was specifically targeted. When depression was the primary focus of the intervention, CBT showed large effect sizes, albeit these conclusions were based on uncontrolled studies.

#### Barker-Collo 2013

This review included English-language studies of any intervention for depression following mild TBI. Some of the papers included had mixed samples and the authors were able to access separate data for participants with mild TBI. Barker-Collo 2013 included all study designs and identified 13 studies of mixed design, with five non-pharmacological interventions (CBT, group education and support, and magnetic field stimulation). Five studies compared an intervention with a control group and eight studies did not, relying on pre-post comparisons. Meta-analyses were conducted which found significant treatment effects in support of the intervention. Meta-analysis of the pre-post studies found a treatment effect of 1.89 (95% CI - 1.20 to 2.58;  $P < 0.001$ ). Meta-analysis of controlled studies (of which only one was a comparison of a non-pharmacological intervention) found a much more modest treatment effect of 0.46 (95% CI -0.44 to 1.36;  $P < 0.001$ ) in favour of the control group. The disparity in findings between controlled and uncontrolled studies is highly relevant and is consistent with the findings of the current review, which identified several studies in which the control group demonstrated improvement throughout the course of data collection.

In conclusion, this review is the only review of RCTs yet published, which focuses specifically on non-pharmacological interventions for people with TBI who demonstrated symptoms, or had a diagnosis, of depression. The findings of the current review are consistent with previous reviews, albeit the inclusion criteria for this review was stricter, and the range of sources searched was wider. Previous reviews identified a multitude of studies, most of which were of lower quality (with the exception of Hoffman 2010), and were therefore excluded in the current review. Because of the reliance on higher quality evidence, the authors of this review have

more confidence in the findings of this review than any previous review.

## AUTHORS' CONCLUSIONS

### Implications for practice

The review did not find compelling evidence in support of any particular intervention that would inform clinical practice. The identified studies did find that some participants responded to interventions, whereas without an intervention, some control-group participants experienced reduction in depression symptoms or remission of diagnoses. It is important when considering an intervention for depression following traumatic brain injury, that clinicians think carefully about what outcomes would be personally meaningful to the patient, their families and other supporters. It is important at the outset to establish the desired outcomes and how these would be measured, and to set up systems so that progress can be evaluated throughout. In this way, despite the absence of a treatment of choice, at least the clinician can be informed whether the patient is improving, and might be able to determine which components of treatment are beneficial for that patient.

### Implications for research

This review has important implications for studies of non-pharmacological interventions for depression following TBI. Primarily, it is critically important that researchers carefully consider the selection criteria for participants. Most of the studies that were identified but not included in the review were rejected either because the selection criteria did not specify a diagnosis of a depressive disorder, there was no cut-off score applied to a clinical measure of depression, or both. A lack of selection criteria that specify the presence of depression is problematic, because it is likely that these studies included participants who were not depressed and therefore would not be expected to show substantial improvement on depression measures. In the clinical setting, it is unlikely they would be offered treatment and therefore their participation in clinical research is of questionable value for addressing the issue of effective treatments for depression after TBI. Therefore, it is recommended that selection of participants is based on their diagnostic status as specified by a recognised diagnostic manual (e.g. DSM-IV; APA 2000). If diagnostic status is not specified as an inclusion criterion, then at the very least, the inclusion criteria should include a clinical cutoff on a recognised measure of depression. Where self-rating scales are used, authors should give careful consideration to using a scale that has widespread use in the general population, and has been proven valid in TBI, such as the Beck Depression Inventory (BDI; Green 2001; Sliwinski 1998), or the Depression Anxiety and Stress Scales (DASS; Ownsworth 2008). It is recommended that self-rating scales are used as secondary outcomes to clinician-rated scales, such as the SCID (e.g.

Ashman 2014). Because it is very difficult to blind participants to the intervention, it is likely that self-rating scales will reflect subjective impressions of the benefit (or otherwise) of interventions.

Some studies were investigated but excluded on the basis that there were mixed samples of TBI and other non-traumatic brain injuries, and separate data were not available for TBI participants. Although non-TBI participants might have been similar to TBI participants in age and demographic factors, they were not directly comparable in terms of their underlying pathology, cognition, behaviour, physical symptoms or adjustment to impairment. Finally, another common reason for exclusion of studies was that the intervention did not target depression specifically, but rather more general concepts, such as 'emotional distress'. As has been discussed, some interventions (particularly CBT) tend to be effective for specific clinical problems and therefore, it is not advisable to set out to treat a broadly-defined clinical presentation, because it appears to weaken the effect of the intervention. An example of this was Simpson 2011, who set out to target hopelessness in relation to suicidality. On the measure of hopelessness, Simpson 2011 found a positive effect in favour of CBT, however, this was not found on a secondary measure of depression.

When designing studies, researchers should give careful consideration to the nature of the intervention given to the control group. In all of the selected studies, there was a lack of an alternative placebo intervention, and therefore intervention participants were unable to be blinded to the intervention they received. Ashman 2014 compared two active psychological interventions that comprised a similar level of therapist contact (i.e. treatment done), and did not find a difference on the main clinician-rated outcome. Other RCTs have been able to include both a wait-list control intervention and a 'sham' treatment intervention so that the impact of the attention of personnel on addressing the clinical problem could be evaluated (e.g. McDonald 2008).

At present, there is a growing pool of intervention studies for depression following TBI. The treatment that showed the larger treatment effect was rTMS plus TCA (He 2004), but there is a need for replication of the He 2004 study, with the addition of a more objective clinician-rated measure and long-term follow-up data. In addition, it would be possible to compare the intervention with a placebo control intervention. An earlier Cochrane review of rTMS reporting the use of a 'sham' TMS intervention amongst the selected studies (Rodriguez-Martin 2001).

The recent studies of psychological interventions found a high percentage of recovery for control participants (Ashman 2014; Bedard 2013; Fann 2015). A criticism of the group designs (including RCTs) is that while an intervention group may or may not respond as a whole to an intervention, this masks interesting individual responses to the intervention. Group studies do not explain why some individuals will respond while others may not. There is concern that structured, manualised treatments that are

investigated in group studies, do not adequately reflect interventions in the 'real world', which are usually tailored to the individual case. In the case of an intervention such as CBT, there are various components that are part of the intervention, but group studies do not distinguish which components of the intervention might be the most effective. The RCTs of psychological interventions were subject to bias due to issues with participation, including a high dropout rate (Ashman 2014; Bedard 2013), a small sample size (Simpson 2011), or an adequate sample size, but a very high refusal rate for referrals to the study (Fann 2015). This suggests that there are many drawbacks to attempting to evaluate a psychological treatment with an RCT design, and that alternative treatment designs, such as a well designed, single case experiment, might provide more useful information about the effectiveness of a particular psychological treatment.

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Shinohara K, Honyashiki M, Imai H, Hunot V, Caldwell DM, Davies P, et al. Behavioural therapies versus other psychological therapies for depression. *Cochrane Database of Systematic Reviews* 2013, Issue 10. [DOI: 10.1002/14651858.CD008696.pub2]

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Slade T, Johnston A, Oakley-Browne MA, Andrews G, Whiteford H. 2007 National Survey of Mental Health and Wellbeing: methods and key findings. *Australian and New Zealand Journal of Psychiatry* 2009;**43**:594–605.

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#### Smith 2010

Smith CA, Hay PP, MacPherson H. Acupuncture for depression. *Cochrane Database of Systematic Reviews* 2010, Issue 1. [DOI: 10.1002/14651858.CD004046.pub3]

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Snell DL, Surgenor LJ, Hay-Smith EJC, Siegert RJ. A systematic review of psychological treatments for mild traumatic brain injury: An update on the evidence. *Journal of Clinical and Experimental Neuropsychology* 2009;**31**:20–38.

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Tuunainen A, Kripke DF, Endo T. Light therapy for non-seasonal depression. *Cochrane Database of Systematic Reviews* 2004, Issue 2. [DOI: 10.1002/14651858.CD004050.pub2]

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Waldron B, Casserly LM, O'Sullivan C. Cognitive behavioural therapy for depression and anxiety in adults with acquired brain injury. What works for whom?. *Neuropsychological Rehabilitation* 2013 [Epub 2012 Nov 5]; **23**(1):64–101. [DOI: 10.1080/09602011.2012.724196]

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\* Indicates the major publication for the study

## CHARACTERISTICS OF STUDIES

### Characteristics of included studies [ordered by study ID]

#### Ashman 2014

Methods	Randomised controlled trial.	
Participants	<p>Seventy-seven people who had sustained a traumatic brain injury who were living in the community. Participants were recruited from an outpatient rehabilitation service, clinic newsletter and word of mouth</p> <p><i>Inclusion criteria:</i> Medically documented traumatic brain injury; current DSM-IV diagnosis of a depressive disorder or Beck Depression Inventory (BDI-II) score greater than 20; 18 to 55 years old</p> <p><i>Exclusion criteria:</i> Presence or history of psychosis, substance abuse, pre-existing neurological disorder, mental retardation, or active suicidality; currently in psychotherapy; commenced or changed antidepressant medication within the past six months</p>	
Interventions	All participants attended 16 sessions of individual treatment over three months. Participants were allocated either for cognitive-behavioural therapy (CBT) or supportive psychotherapy (SPT)	
Outcomes	<p><i>Primary outcome measure:</i> Presence of a DSM-IV depressive mood disorder assessed by the Structured Clinical Interview for DSM-IV (SCID)</p> <p><i>Secondary outcome measures:</i> Beck Depression Inventory - second edition (BDI-II) Anxiety disorder and substance abuse modules of the SCID State-Trait Anxiety Inventory (STAI) Life-3 Interpersonal Support Evaluation List (ISEL) Life Experiences Survey (LES)</p>	
Notes		
<b><i>Risk of bias</i></b>		
<b>Bias</b>	<b>Authors' judgement</b>	<b>Support for judgement</b>
Random sequence generation (selection bias)	Low risk	Computer-generated random sequence generation.
Allocation concealment (selection bias)	Low risk	Random number sequence was concealed in pre-sealed individual envelopes
Blinding of participants and personnel (performance bias) All outcomes	High risk	Due to disparate experimental conditions, blinding of participants and personnel was not possible

**Ashman 2014** (Continued)

Blinding of outcome assessment (detection bias) All outcomes	Low risk	Primary outcome measure was a clinical scale, applied by a clinician, who was blind to the treatment
Incomplete outcome data (attrition bias) All outcomes	High risk	Of 77 participants randomised to a treatment, only 43 completed the study. Twenty-two dropped out after baseline assessment and a further 12 participants did not complete the study
Selective reporting (reporting bias)	Low risk	The published study is consistent with an earlier conference abstract (Ashman 2012) and the protocol registered on <a href="http://Trialscentral.org">Trialscentral.org</a> . The study was registered on <a href="http://clinicaltrials.gov">clinicaltrials.gov</a> , study ID: NCT00211835
Other bias	Unclear risk	-

**Bedard 2013**

Methods	Multi-centre randomised controlled trial, intervention and wait-list control groups with cross-over design
Participants	Seventy-six people who had sustained traumatic brain injury completed the study. Recruitment sources: community clinics, media advertisements, non-government organisations and through personal contact with rehabilitation practitioners <i>Inclusion criteria:</i> Evidence of depression (score of 16 or higher on the BDI-II); ability to read and speak English; age 18 or over; and having completed all standard treatments for the injury <i>Exclusion criteria:</i> Presence of unusual psychological processes such as psychosis, suicide ideation, substance abuse or major concurrent medical illnesses
Interventions	For intervention participants, this was a 10-week program of weekly 90-minute group sessions plus recommended daily meditation for 20 to 30 minutes. The treatment followed a standard manual for mindfulness-based cognitive therapy, however, components were modified to suit people with brain injury. After the intervention group had completed treatment, the wait list group was offered treatment, the outcomes of which are reported separately
Outcomes	<i>Primary outcome measures:</i> Beck Depression Inventory - second edition (BDI-II) Patient Health Questionnaire (PHQ) Symptom Checklist 90 Revised (SCL-90R) <i>Secondary outcome measures:</i> Philadelphia Mindfulness Scale Toronto Mindfulness Scale
Notes	
<b>Risk of bias</b>	

**Bedard 2013** (Continued)

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	Randomisation was conducted by a statistician who was independent of the clinicians and site investigators. The statistician used minimisation to ensure balance at baseline, between the groups, on a key outcome measure (Beck Depression Inventory). These measures present low risk of selection bias. However, five participants at one site were allocated to the intervention due to low participant numbers at that site
Allocation concealment (selection bias)	Low risk	Allocation occurred off site and without the knowledge of the site investigators or group facilitators
Blinding of participants and personnel (performance bias) All outcomes	High risk	Blinding of participants and personnel not possible due to one intervention being an active intervention, while the other was a passive wait-list control
Blinding of outcome assessment (detection bias) All outcomes	High risk	The outcome measures were self-report questionnaires and therefore, subject to high risk of bias due to the participants' knowledge to which intervention they had been allocated
Incomplete outcome data (attrition bias) All outcomes	High risk	There was substantial dropout from the study (19 of 57 participants allocated to intervention and 10 of 48 allocated to wait-list). The higher dropout from the intervention group could have increased bias as it is possible these participants had greater symptoms of depression, the primary outcome of the study
Selective reporting (reporting bias)	Low risk	Outcome measures were stated in a study protocol registered on the <a href="http://www.trialscentral.org">Trialscentral.org</a> website (NCT00745940). These outcomes were consistent with the published results
Other bias	Unclear risk	-

**Fann 2015**

Methods	Randomised controlled trial.	
Participants	<p>One hundred adults with TBI and a current diagnosis of major depressive disorder (MDD). Recruitment was conducted at community and clinical settings serving people with TBI, and through referrals from clinicians</p> <p><i>Inclusion criteria:</i> English-speaking people over 18 years old, who had a documented history of mild to severe TBI, including criteria relating to Glasgow Coma Score (GCS), imaging abnormalities or duration of post-traumatic amnesia (PTA). All participants had to meet diagnostic criteria for MDD with the use of the Structured Clinical Interview for Depression (SCID) and demonstrate symptoms of depression over the clinical cutoff on the Patient Health Questionnaire (PHQ-9)</p> <p><i>Exclusion criteria:</i> No stable home or access to telephone; history of diagnosis of schizophrenia; evidence of bipolar disorder, psychosis or suicidal intent, or current alcohol or drug dependence; currently receiving or planning to start evidence-based psychotherapy for depression during the study; commencing or adjusting anti-depressant medication during the study; or severe cognitive impairment as defined by scores below cutoff on specific neuropsychological tests</p>	
Interventions	<p>The intervention comprised a manualised CBT program written to be delivered by telephone. It was modified for TBI participants with an expansion in duration from eight weekly sessions to 12 and the addition of care management procedures for the life changes experienced by this population. Motivational interviewing was used to engage participants in treatment. The session material was presented in smaller portions, more slowly, and with greater repetition. Participants were provided with a workbook with in-session materials and between-session assignments. Two authors provided treatment and 10% of sessions were subject to fidelity checks</p>	
Outcomes	<p><i>Primary outcome measures:</i> Hamilton Depression Rating Scale (HAMD-17) Symptom Checklist-20 (SCL-20)</p> <p><i>Secondary outcome measures:</i> MDD criteria based on the SCID Patient Global Impression (PGI) Satisfaction with Depression Care Working Alliance Inventory-Short Form Sheehan Disability Scale MOS Short Form Health Questionnaire (SF-36) Head Injury Symptom Checklist</p>	
Notes		
<b><i>Risk of bias</i></b>		
<b>Bias</b>	<b>Authors' judgement</b>	<b>Support for judgement</b>
Random sequence generation (selection bias)	Low risk	All participants were randomised to an intervention. In order to increase participation in the study, the authors used a choice-stratified approach in which participants had the option of choosing to be randomised to any

**Fann 2015** (Continued)

		intervention (CBT-T vs CBT-IP vs usual care), or one CBT intervention (CBT-T or CBT-IP) vs usual care. The random sequence was computer-generated
Allocation concealment (selection bias)	Low risk	Group allocation was centrally assigned following enrolment in the study
Blinding of participants and personnel (performance bias) All outcomes	High risk	Because of the nature of the interventions, it was not possible to blind participants and personnel
Blinding of outcome assessment (detection bias) All outcomes	High risk	Assessment was conducted over the telephone by trained study staff who were blind to randomisation status. However, most of the outcome measures rely on participant self-report and therefore are subject to bias due to awareness of allocation. Even the HAMD, which is a clinician-report scale, does rely upon patient self-report for many items, and therefore cannot be considered to be an objective measure
Incomplete outcome data (attrition bias) All outcomes	Low risk	Eighty-six percent of participants provided data at follow-up
Selective reporting (reporting bias)	Low risk	The outcome measures reported in the results section are consistent with those in the methods section. The trial protocol was registered in clinicaltrials.gov (identifier: NCT00878150). All primary outcomes and most secondary outcomes are reported in the final publication, albeit with some substitution of secondary measures prior to commencing data collection
Other bias	Unclear risk	-

**He 2004**

Methods	Randomised controlled trial.
Participants	Sixty-four brain injured patients were identified from the Department of Neurosurgery and Rehabilitation, Affiliated Hospital of Luzhou Medical College <i>Inclusion criteria:</i> First time experiencing cranial head injury and confirmed through CT or MRI scans; score greater than 8 on the Hamilton Rating Scale for Depression (HAMD) <i>Exclusion criteria:</i> Aphasia, unconscious, severe dementia, drug and alcohol abuse, severe disability
Interventions	All participants received oral tricyclic antidepressant drugs, with only the intervention group also receiving repetitive transcranial magnetic stimulation (rTMS) treatment. Consent was obtained from the patient or family members to receive the treatments. Maglite Compact magnetic stimulation was used with a coil diameter of 12 cm, maximum in-

**He 2004** (Continued)

	tensity of 1.2 T, pulse time limit of 100 $\mu$ s. Quote: "Patients, in a seated position during treatment, received 60% of the maximum intensity (0.72 T), with bilateral stimulation of the frontal lobes, 30 times to each side, with a frequency of 0.5 Hz, each day consecutively for 5 d, which equals to one treatment session. Treatments were given on a 2-day interval, with each patient receiving 4 treatment sessions." p 6045	
Outcomes	Pre- and post-intervention HAMD score. Pre- and post-intervention Mini-Mental State Examination (MMSE) score Plasma monoamine neurotransmitters concentrations.	
Notes		
<b>Risk of bias</b>		
<b>Bias</b>	<b>Authors' judgement</b>	<b>Support for judgement</b>
Random sequence generation (selection bias)	Unclear risk	Authors used a predetermined list for allocation, but did not state the method of sequence generation
Allocation concealment (selection bias)	Unclear risk	Method of allocation was not specified.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Participants receiving the intervention were aware that they were receiving rTMS. There was no sham intervention that might prevent the control group participants from recognising that they were not getting the treatment
Blinding of outcome assessment (detection bias) All outcomes	High risk	Different personnel, blinded to the intervention, conducted the outcome assessments, however, the primary outcome measures were self-report scales, and therefore subject to bias since the participants were aware of the intervention to which they were assigned
Incomplete outcome data (attrition bias) All outcomes	Low risk	Of the 64 participants allocated to groups, only one failed to complete data collection
Selective reporting (reporting bias)	Unclear risk	Insufficient information available.
Other bias	Unclear risk	-

**Hoffman 2010**

Methods	Randomised controlled trial.
Participants	Eighty participants were recruited through posted and online advertisements in local rehabilitation clinics, newspapers, and websites. Local rehabilitation physicians and psychologists were given information and flyers for the study <i>Inclusion criteria:</i> Self-reported TBI, severe enough to have required medical evaluation or hospital admission immediately after injury; TBI from 6 months to 5 years prior to

**Hoffman 2010** (Continued)

	<p>enrolment; score of 5 or more on the Patient Health Questionnaire-9 (PHQ-9), indicating at least a mild level of depressive symptoms; sufficient cognitive ability to maintain an exercise log and independently participate in the study, or have the involvement of a support person to facilitate involvement</p> <p><i>Exclusion criteria:</i> Having a medical condition that would preclude or limit exercise; current suicidal ideation with intent or plan; current pregnancy; current regular exercise program three times a week or more; any physical barrier to the use of standard aerobic exercise equipment</p>	
Interventions	<p>The intervention was supervised exercise training once a week in a gymnasium with a research education trainer and certified athletic trainer. Each session included; 15 minutes of education on an exercise-related topic; 15 minutes of warm-up exercises consisting of stretching and walking; 30 minutes of aerobic exercise. In addition the intervention included a home program, whereby each participant was asked to perform 30 minutes of aerobic exercise at least 4 times a week, in addition to the supervised exercise session. Control group participants were given instruction that they would be contacted for assessment after 10 weeks. They were given no particular instructions regarding exercise</p>	
Outcomes	<p><i>Primary outcome measure:</i> Beck Depression Inventory (BDI)</p> <p><i>Secondary outcome measures:</i> Brief Pain Inventory Pittsburgh Sleep Inventory Head Injury Symptom Checklist SF-12 Health Survey Craig Handicap Assessment and Reporting Technique - Short Form (CHART-SF) Perceived Quality of Life (PQOL)</p>	
Notes		
<b><i>Risk of bias</i></b>		
<b>Bias</b>	<b>Authors' judgement</b>	<b>Support for judgement</b>
Random sequence generation (selection bias)	Low risk	Sequence was created using a random number generation program (personal communication with primary author)
Allocation concealment (selection bias)	Low risk	Use of sealed envelopes to ensure blinding.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Blinding not possible because study was a comparison between an active intervention (exercise program) and a wait-list control
Blinding of outcome assessment (detection bias) All outcomes	High risk	Outcome assessment was completed by a research assistant blind to group allocation (personal communication with primary author), however, the primary outcome measure was a self-report scale and therefore subject to bias since the participants were aware of the intervention



**Hoffman 2010** (Continued)

		to which they were assigned
Incomplete outcome data (attrition bias) All outcomes	Low risk	Eighty participants were randomised, with 76 completing the outcome assessment. Missing outcome data were balanced between groups, with a similar reason for missing data (participants unable to be contacted for follow-up)
Selective reporting (reporting bias)	Low risk	Table 2 reports data on each measure, for each group, at each time-point
Other bias	Unclear risk	-

**Simpson 2011**

Methods	RCT with wait-list control, cross-over design.	
Participants	Seventeen patients recruited from the Liverpool (Australia) Hospital brain injury community team caseload <i>Inclusion:</i> severe TBI (PTA > 1 day), aged 18 years or older, moderate to severe levels of hopelessness, suicidal ideation, or both <i>Exclusion:</i> severe neuropsychological impairments in cognitive or language functions, extremely challenging behaviour that would preclude compliance with the study protocol, and non-fluency in English	
Interventions	Cognitive-behavioural therapy delivered via a 20-hour manualised group-based programme, delivered in 10 weekly 2-hour sessions	
Outcomes	<i>Primary outcome measures:</i> Beck Hopelessness Scale (BHS) Beck Scale for Suicide Ideation (BSS) Hospital Anxiety and Depression Scale (HADS) <i>Secondary outcome measures:</i> Herth Hope Index Rosenberg Self-Esteem Scale Social Problem Solving Inventory-Revised (SPSI-R) <i>Timepoints measured:</i> Baseline At completion of treatment (10 weeks after baseline) 3 months after completion of treatment	
Notes		
<b><i>Risk of bias</i></b>		
<b>Bias</b>	<b>Authors' judgement</b>	<b>Support for judgement</b>

**Simpson 2011** (Continued)

Random sequence generation (selection bias)	Low risk	Block randomisation: groups of 4 participants allocated to an intervention, using a computer-generated set of random numbers
Allocation concealment (selection bias)	Low risk	Allocation to intervention conducted off-site and allocation was concealed
Blinding of participants and personnel (performance bias) All outcomes	High risk	The study interventions were either an active treatment or a wait-list control, and therefore, blinding of participants and personnel was not possible
Blinding of outcome assessment (detection bias) All outcomes	High risk	Assessments at completion of treatment and at 3-month follow-up were conducted by an independent assessor who was blind to the intervention group. Participants were asked not to disclose their intervention group to the assessor. The independent assessor was asked to record any inadvertent disclosure of the participants' intervention group. However, the primary outcome measures were self-report scales and therefore, subject to bias since the participants were aware of the intervention group to which they were assigned
Incomplete outcome data (attrition bias) All outcomes	Low risk	Seventeen participants' were randomised to groups. Only one subject withdrew prior to the final assessment time point
Selective reporting (reporting bias)	Low risk	Primary author provided the study protocol, which showed that all outcomes collected were reported
Other bias	High risk	Small sample size (intervention group, N = 8 and control group, N = 9)

**Characteristics of excluded studies** [ordered by study ID]

Study	Reason for exclusion
Anson 2006	Inclusion criteria did not specify diagnosis of depression, or clinical cutoff for a measure of depression

*(Continued)*

Bateman 2001	Inclusion criteria did not specify diagnosis of depression, or clinical cutoff for a measure of depression. Intervention was not for depression
Bell 2008	Inclusion criteria did not specify diagnosis of depression, or clinical cutoff for a measure of depression. Intervention was not specifically for depression
Bombardier 2009	Inclusion criteria did not specify diagnosis of depression, or clinical cutoff for a measure of depression
Bradbury 2008	Not a randomised controlled trial, but a matched controlled trial. Participants were allocated to groups by logistical considerations. Inclusion criteria did not specify diagnosis of depression, or clinical cutoff for a measure of depression. Intervention was not for depression. Sample was not limited to people with TBI, although the authors were able to provide separate data just for participants with TBI
Carey 2008	Inclusion criteria did not specify diagnosis of depression, or clinical cutoff for a measure of depression
Cullen 2007	Inclusion criteria did not specify diagnosis of depression, or clinical cutoff for a measure of depression Sample was not limited to traumatic brain injury.
Driver 2009	Inclusion criteria did not specify diagnosis of depression, or clinical cutoff for a measure of depression
Fleming 2009	Inclusion criteria did not specify diagnosis of depression, or clinical cutoff for a measure of depression Sample was not limited to traumatic brain injury.
Geurtsen 2008	Inclusion criteria did not specify diagnosis of depression, or clinical cutoff for a measure of depression
Ghaffar 2006	Inclusion criteria did not specify diagnosis of depression, or clinical cutoff for a measure of depression. Intervention was not for depression
Huckans 2010	Inclusion criteria did not specify diagnosis of depression, or clinical cutoff for a measure of depression. Intervention was not for depression
Leonard 2004	Inclusion criteria did not specify diagnosis of depression, or clinical cutoff for a measure of depression. Intervention was not for depression
McDonald 2008	Inclusion criteria did not specify diagnosis of depression, or clinical cutoff for a measure of depression. Intervention was not for depression Sample was not limited to people with TBI.
Powell 2002	Inclusion criteria did not specify diagnosis of depression, or clinical cutoff for a measure of depression
Ruff 1990	Inclusion criteria did not specify diagnosis of depression, or clinical cutoff for a measure of depression. Intervention was not for depression
Smith 1994	Sample was not limited to people with TBI.
Stocksmeier 1992	Sample was not limited to people with TBI.

(Continued)

Stoll 1999	Inclusion criteria did not specify diagnosis of depression, or clinical cutoff for a measure of depression
Struchen 2011	Inclusion criteria did not specify diagnosis of depression, or clinical cutoff for a measure of depression
Sun 2008	Pharmacological intervention.
Teasdale 1995	Intervention was not for depression. Sample was not limited to people with TBI. Not a randomised controlled trial.
Tiersky 2005	Inclusion criteria did not specify diagnosis of depression, or clinical cutoff for a measure of depression. Intervention was not for depression
Wade 2006	Inclusion criteria did not specify diagnosis of depression, or clinical cutoff for a measure of depression. Intervention was not for depression
Wade 2008	Inclusion criteria did not specify diagnosis of depression, or clinical cutoff for a measure of depression. Intervention was not for depression

**Characteristics of studies awaiting assessment** *[ordered by study ID]***NCT01039857**

Methods	
Participants	
Interventions	
Outcomes	
Notes	This study was terminated early. The review authors are trying to obtain further information about the study

**Characteristics of ongoing studies** *[ordered by study ID]***Clark 2014**

Trial name or title	A randomised controlled trial of a modified group cognitive behavioural intervention for depressed mood following traumatic brain injury
Methods	Randomised controlled trial.
Participants	Persons with medically documented, complicated mild, moderate, or severe TBI, who had clinically significant depressive symptoms

**Clark 2014** (Continued)

Interventions	<i>Intervention:</i> modified cognitive behavioural therapy (6 sessions). <i>Control:</i> support group (6 sessions).
Outcomes	Measures of depression, perceived stress.
Starting date	Not known.
Contact information	Allison Clark, Baylor College of Medicine, Houston, TX, USA.
Notes	The study author was in contact with the Injuries Group editorial team on 21 October 2015 to say that the study has been completed, and the final report has been submitted to a medical journal for publication

**NCT00531258**

Trial name or title	TMS in the treatment of the sequelae of traumatic brain injury
Methods	Randomised controlled trial, intervention and control groups
Participants	Currently recruiting adults aged 18 to 60 with a history of TBI, who meet DSM-IV-TR criteria for major depressive disorder and score 20 or above on the Montgomery-Asberg Rating Scale
Interventions	Repetitive transcranial magnetic stimulation (rTMS) versus sham rTMS
Outcomes	Unknown
Starting date	October 2007
Contact information	Paul Fitzgerald, paul.fitzgerald@monash.edu
Notes	Study identification number on clinicaltrials.gov: NCT00531258

**NCT01691378**

Trial name or title	Window to hope: Preliminary results from a randomised controlled trial (RCT) of a psychological treatment for hopelessness among US veterans with traumatic brain injury (TBI)
Methods	Randomised controlled cross-over study.
Participants	<ul style="list-style-type: none"> <li>● Age between 18 and 65</li> <li>● Determination of positive history of moderate or severe TBI</li> <li>● Beck Hopelessness Scale score of 9 or greater</li> <li>● Ability to adequately respond to questions regarding the informed consent procedure</li> </ul>
Interventions	'Window to Hope' group psychological treatment versus wait-list control

**NCT01691378** (Continued)

Outcomes	<i>Primary:</i> Change in Beck Hopelessness Scale (BHS). <i>Secondary:</i> (1) Change in Beck Scale for Suicidal Ideation (BSS), (2) Change in Beck Depression Inventory (BDI-II)
Starting date	January 2012
Contact information	Lisa Brenner, VA Eastern Colorado Health Care System, Military Suicide Research Consortium (MSRC)
Notes	Study identification number on clinicaltrials.gov: NCT01691378

**NCT02367521**

Trial name or title	Repetitive Transcranial Magnetic Stimulation (rTMS) for the Treatment of Depression & Other Neuropsychiatric Symptoms After Traumatic Brain Injury (TBI) (rTMS TBI)
Methods	Randomised controlled trial.
Participants	TBI patients who score greater than 10 on the Hamilton Depression Scale - 17 item
Interventions	Low Frequency Right sided repetitive transcranial magnetic stimulation (LFR rTMS) versus sham control
Outcomes	Primary outcome: Number of participants with improvement in depressive symptoms using the HAM-D scale, at 16 weeks follow-up. (To determine the effectiveness of LFR rTMS for the treatment of post-TBI depression and suicidal ideation.) Secondary outcome: Number of participants with improvement in overall functioning using the CGI scale, at 16 weeks follow-up. (To determine the effectiveness of LFR rTMS for the treatment of post traumatic stress disorder, sleep disturbance and cognitive deficits.)
Starting date	March 2015
Contact information	Vani Rao, MD vrao@jhmi.edu Alex Vassila avassil1@jhmi.edu
Notes	Sponsors and Collaborators: Johns Hopkins University, and United States Department of Defense

## DATA AND ANALYSES

### Comparison 1. CBT versus control

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Major depressive disorder (MDD) on the structured clinical interview for depression (SCID) scale	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
2 MDD on SCID long term follow up	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
3 Depression scales	3	146	Std. Mean Difference (IV, Random, 95% CI)	-0.14 [-0.47, 0.19]
4 Depression scales long term follow up	3	165	Std. Mean Difference (IV, Random, 95% CI)	-0.02 [-0.33, 0.29]
5 Secondary depression measure - SCL20 or SCL90R	2	175	Std. Mean Difference (IV, Random, 95% CI)	-0.15 [-0.45, 0.15]
6 SCL20 long term follow up	1		Std. Mean Difference (IV, Random, 95% CI)	Totals not selected
7 Secondary depression measure - PGI	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
8 PGI long term follow up	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
9 Secondary measure - Dissatisfaction with depression care	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
10 Secondary depression measure - PHQ	1		Std. Mean Difference (IV, Random, 95% CI)	Totals not selected
11 Beck Hopelessness Scale (BHS)	1		Std. Mean Difference (IV, Random, 95% CI)	Totals not selected
12 Beck Scale for Suicide Ideation	1		Std. Mean Difference (IV, Random, 95% CI)	Totals not selected
13 Rosenberg Self-Esteem Scale	1		Std. Mean Difference (IV, Random, 95% CI)	Totals not selected
14 Treatment drop-outs	3	222	Risk Ratio (M-H, Random, 95% CI)	1.20 [0.57, 2.54]

### Comparison 2. CBT versus SPT

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 MDD present on SCID following intervention	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
2 Beck Depression Inventory (BDI)	1		Std. Mean Difference (IV, Random, 95% CI)	Totals not selected
3 Life 3 - Quality of Life	1		Std. Mean Difference (IV, Random, 95% CI)	Totals not selected
4 Treatment drop-outs	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected

### Comparison 3. Transcranial magnetic stimulation plus TCA versus TCA alone

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Hamilton Rating Scale for Depression (HAM-D)	1		Std. Mean Difference (IV, Random, 95% CI)	Totals not selected
2 Mini Mental State Examination (MMSE)	1		Std. Mean Difference (IV, Random, 95% CI)	Totals not selected
3 Serotonin (5-HT) levels	1		Std. Mean Difference (IV, Random, 95% CI)	Totals not selected
4 Noradrenaline	1		Std. Mean Difference (IV, Random, 95% CI)	Totals not selected
5 Treatment dropouts	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected

### Comparison 4. Supervised exercise versus exercise as usual

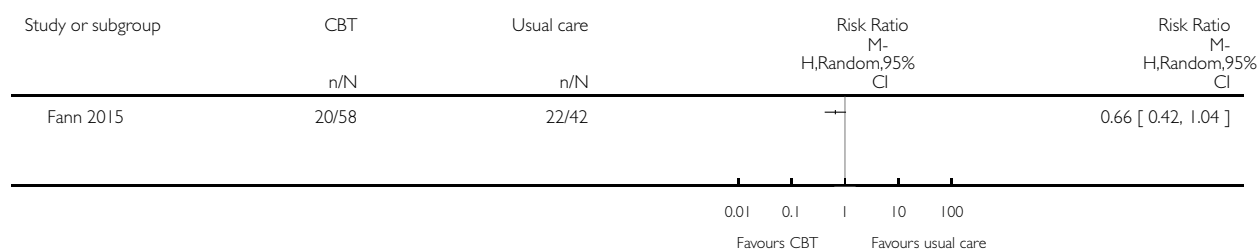
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Beck Depression Inventory (BDI)	1		Std. Mean Difference (IV, Random, 95% CI)	Totals not selected
2 Treatment dropouts	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected

#### Analysis 1.1. Comparison 1 CBT versus control, Outcome 1 Major depressive disorder (MDD) on the structured clinical interview for depression (SCID) scale.

Review: Non-pharmacological interventions for depression in adults and children with traumatic brain injury

Comparison: 1 CBT versus control

Outcome: 1 Major depressive disorder (MDD) on the structured clinical interview for depression (SCID) scale



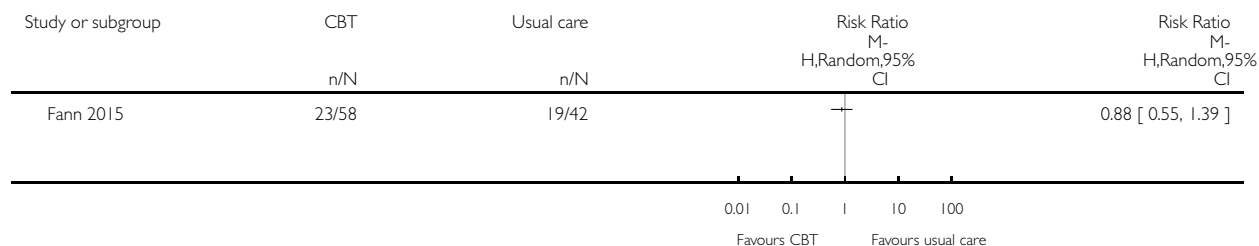


### Analysis 1.2. Comparison 1 CBT versus control, Outcome 2 MDD on SCID long term follow up.

Review: Non-pharmacological interventions for depression in adults and children with traumatic brain injury

Comparison: 1 CBT versus control

Outcome: 2 MDD on SCID long term follow up

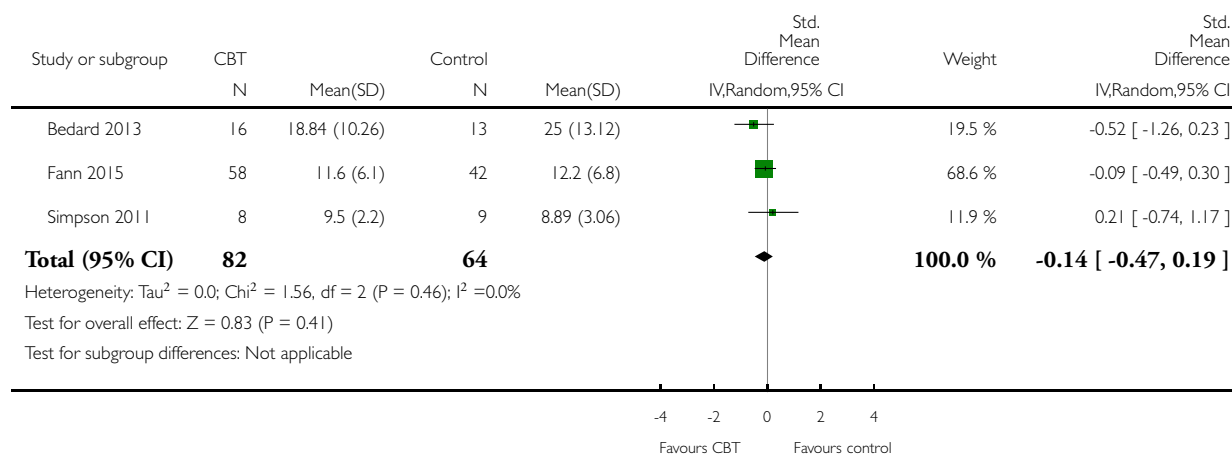


### Analysis 1.3. Comparison 1 CBT versus control, Outcome 3 Depression scales.

Review: Non-pharmacological interventions for depression in adults and children with traumatic brain injury

Comparison: 1 CBT versus control

Outcome: 3 Depression scales

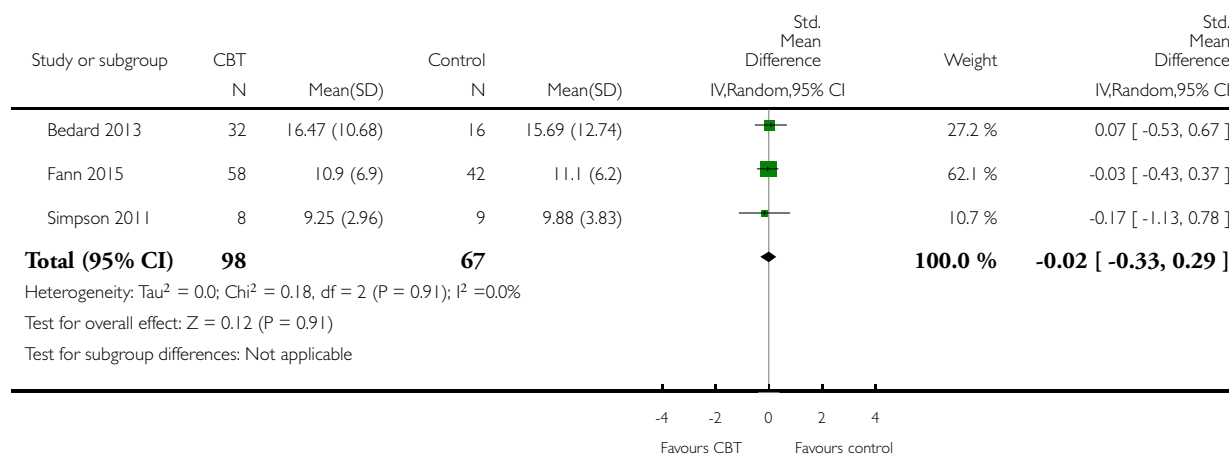


**Analysis 1.4. Comparison 1 CBT versus control, Outcome 4 Depression scales long term follow up.**

Review: Non-pharmacological interventions for depression in adults and children with traumatic brain injury

Comparison: 1 CBT versus control

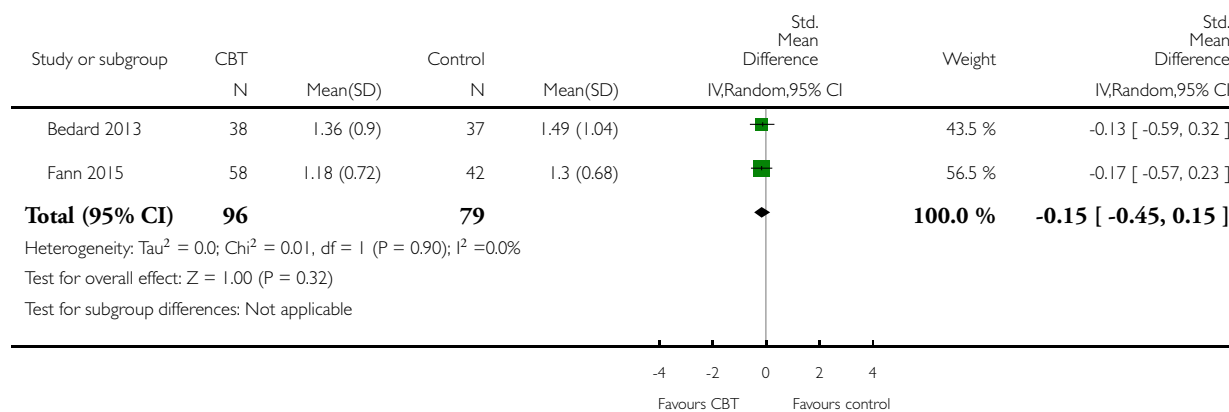
Outcome: 4 Depression scales long term follow up

**Analysis 1.5. Comparison 1 CBT versus control, Outcome 5 Secondary depression measure - SCL20 or SCL90R.**

Review: Non-pharmacological interventions for depression in adults and children with traumatic brain injury

Comparison: 1 CBT versus control

Outcome: 5 Secondary depression measure - SCL20 or SCL90R

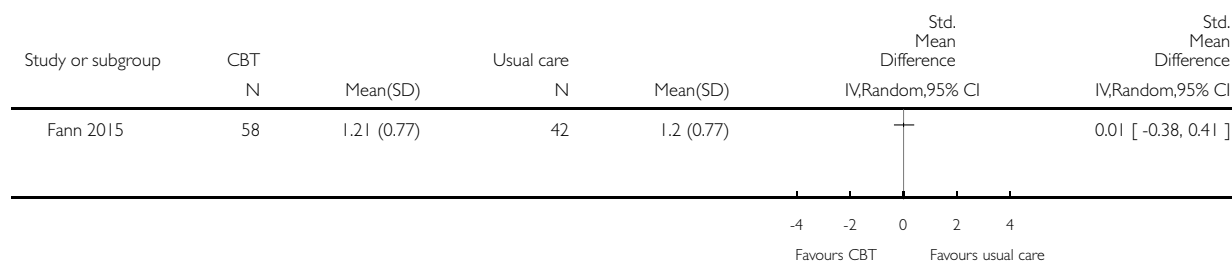


### Analysis 1.6. Comparison 1 CBT versus control, Outcome 6 SCL20 long term follow up.

Review: Non-pharmacological interventions for depression in adults and children with traumatic brain injury

Comparison: 1 CBT versus control

Outcome: 6 SCL20 long term follow up

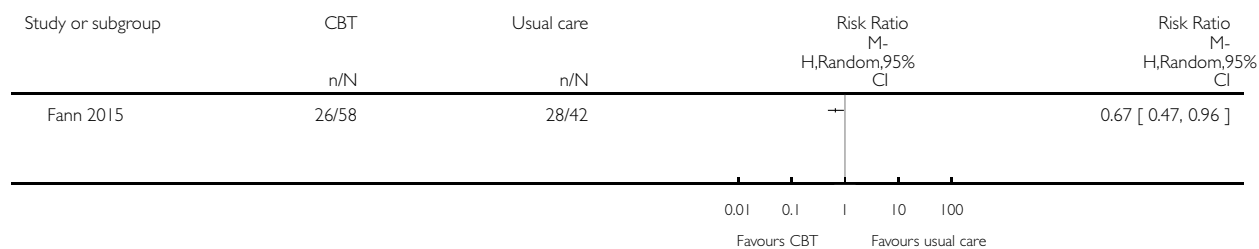


### Analysis 1.7. Comparison 1 CBT versus control, Outcome 7 Secondary depression measure - PGI.

Review: Non-pharmacological interventions for depression in adults and children with traumatic brain injury

Comparison: 1 CBT versus control

Outcome: 7 Secondary depression measure - PGI

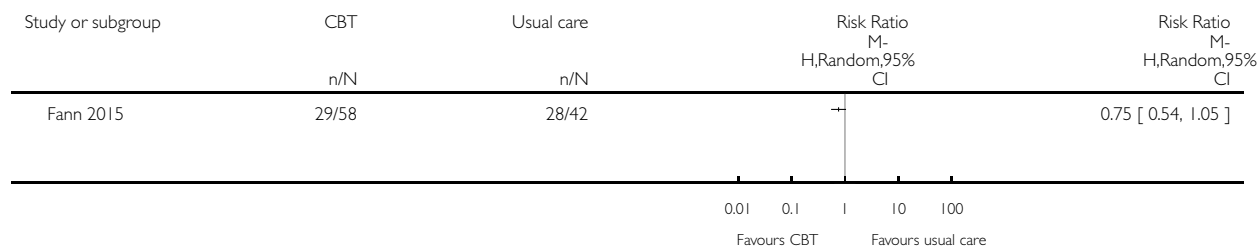


### Analysis 1.8. Comparison 1 CBT versus control, Outcome 8 PGI long term follow up.

Review: Non-pharmacological interventions for depression in adults and children with traumatic brain injury

Comparison: 1 CBT versus control

Outcome: 8 PGI long term follow up

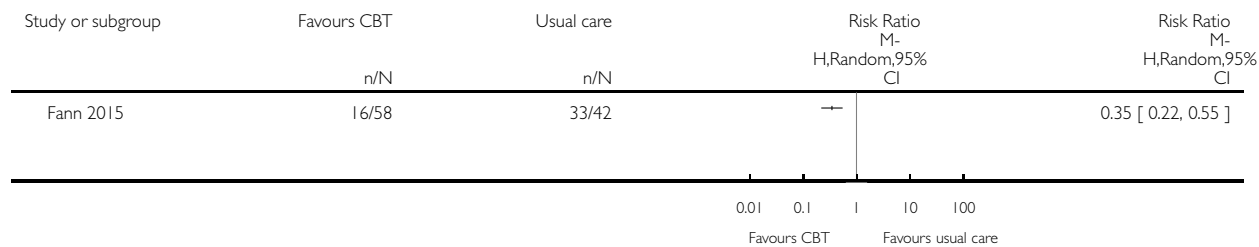


### Analysis 1.9. Comparison 1 CBT versus control, Outcome 9 Secondary measure - Dissatisfaction with depression care.

Review: Non-pharmacological interventions for depression in adults and children with traumatic brain injury

Comparison: 1 CBT versus control

Outcome: 9 Secondary measure - Dissatisfaction with depression care

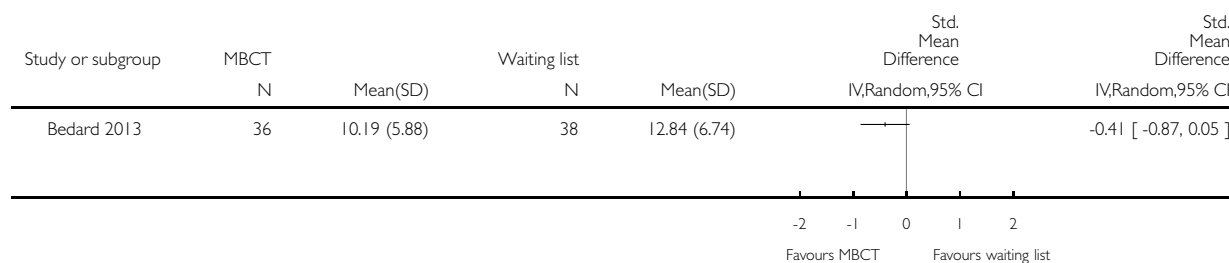


**Analysis 1.10. Comparison 1 CBT versus control, Outcome 10 Secondary depression measure - PHQ.**

Review: Non-pharmacological interventions for depression in adults and children with traumatic brain injury

Comparison: 1 CBT versus control

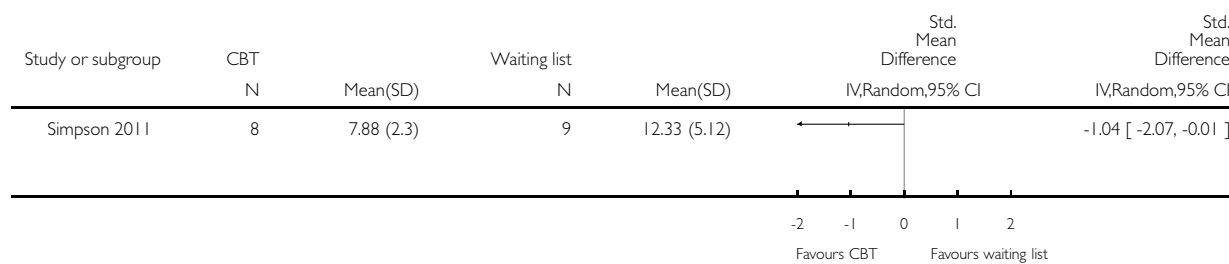
Outcome: 10 Secondary depression measure - PHQ

**Analysis 1.11. Comparison 1 CBT versus control, Outcome 11 Beck Hopelessness Scale (BHS).**

Review: Non-pharmacological interventions for depression in adults and children with traumatic brain injury

Comparison: 1 CBT versus control

Outcome: 11 Beck Hopelessness Scale (BHS)

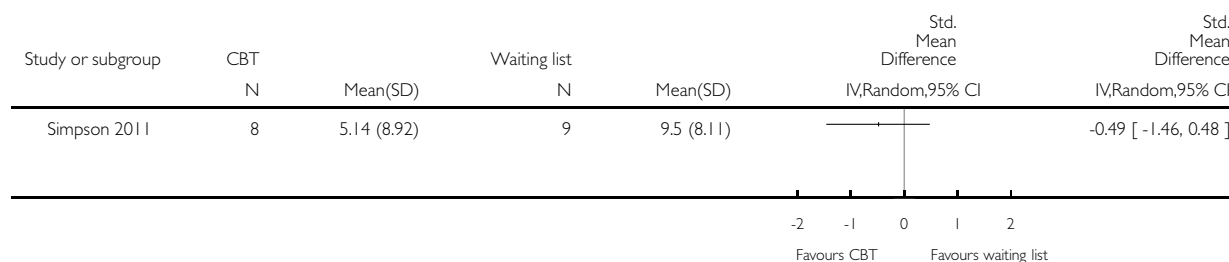


### Analysis 1.12. Comparison 1 CBT versus control, Outcome 12 Beck Scale for Suicide Ideation.

Review: Non-pharmacological interventions for depression in adults and children with traumatic brain injury

Comparison: 1 CBT versus control

Outcome: 12 Beck Scale for Suicide Ideation

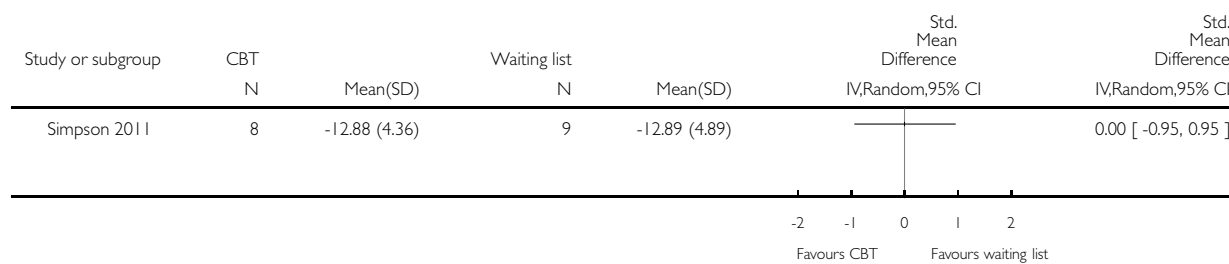


### Analysis 1.13. Comparison 1 CBT versus control, Outcome 13 Rosenberg Self-Esteem Scale.

Review: Non-pharmacological interventions for depression in adults and children with traumatic brain injury

Comparison: 1 CBT versus control

Outcome: 13 Rosenberg Self-Esteem Scale

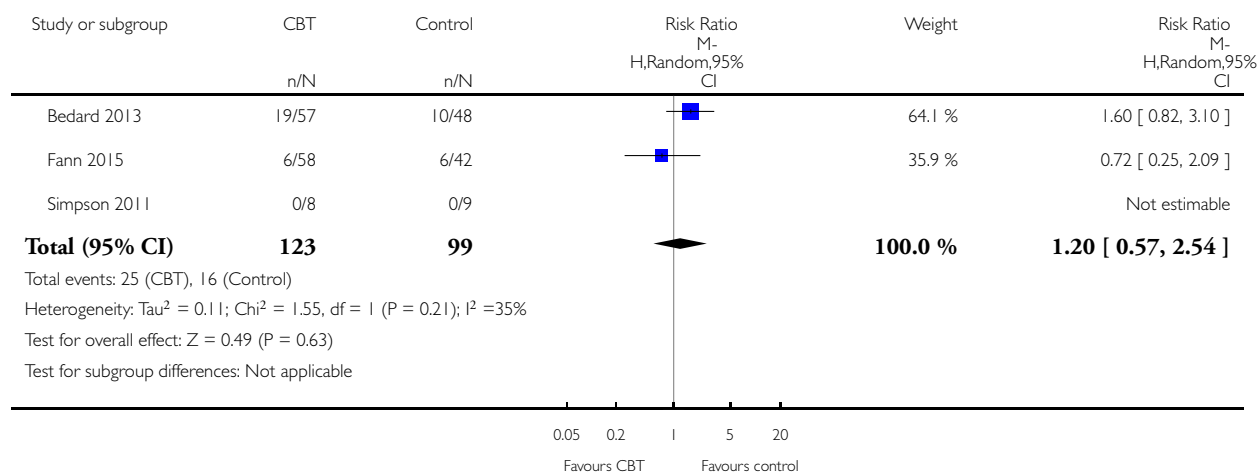


**Analysis 1.14. Comparison 1 CBT versus control, Outcome 14 Treatment drop-outs.**

Review: Non-pharmacological interventions for depression in adults and children with traumatic brain injury

Comparison: 1 CBT versus control

Outcome: 14 Treatment drop-outs

**Analysis 2.1. Comparison 2 CBT versus SPT, Outcome 1 MDD present on SCID following intervention.**

Review: Non-pharmacological interventions for depression in adults and children with traumatic brain injury

Comparison: 2 CBT versus SPT

Outcome: 1 MDD present on SCID following intervention

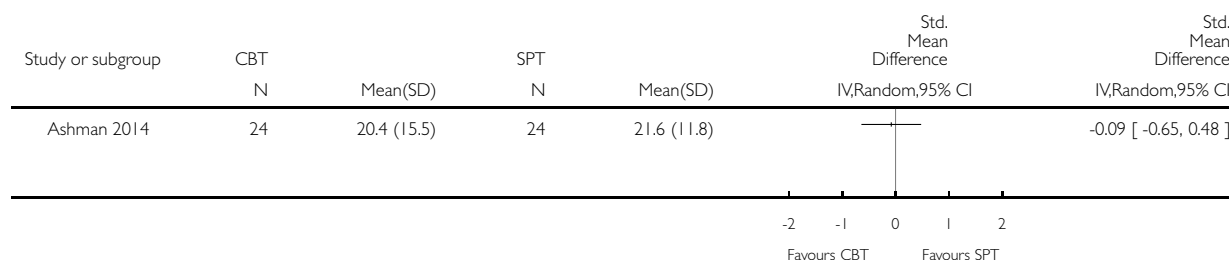


### Analysis 2.2. Comparison 2 CBT versus SPT, Outcome 2 Beck Depression Inventory (BDI).

Review: Non-pharmacological interventions for depression in adults and children with traumatic brain injury

Comparison: 2 CBT versus SPT

Outcome: 2 Beck Depression Inventory (BDI)

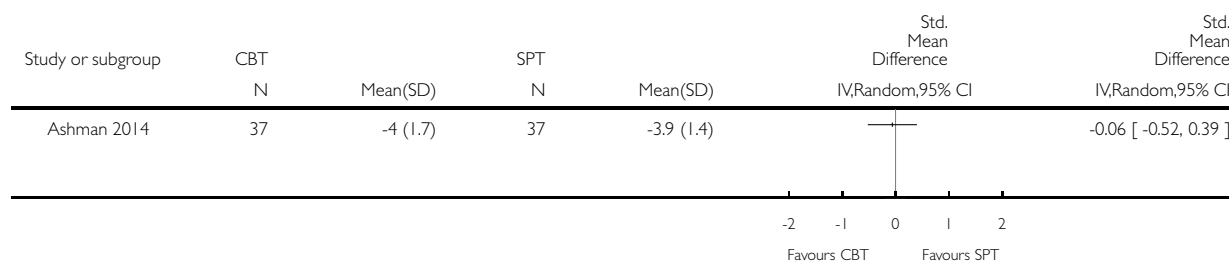


### Analysis 2.3. Comparison 2 CBT versus SPT, Outcome 3 Life 3 - Quality of Life.

Review: Non-pharmacological interventions for depression in adults and children with traumatic brain injury

Comparison: 2 CBT versus SPT

Outcome: 3 Life 3 - Quality of Life



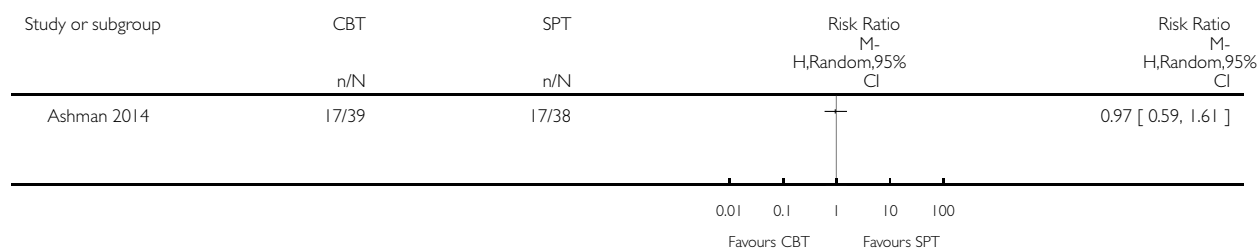


### Analysis 2.4. Comparison 2 CBT versus SPT, Outcome 4 Treatment drop-outs.

Review: Non-pharmacological interventions for depression in adults and children with traumatic brain injury

Comparison: 2 CBT versus SPT

Outcome: 4 Treatment drop-outs

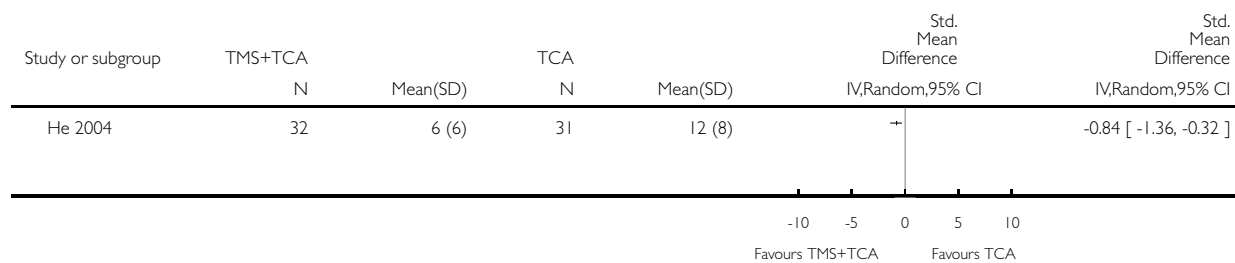


### Analysis 3.1. Comparison 3 Transcranial magnetic stimulation plus TCA versus TCA alone, Outcome 1 Hamilton Rating Scale for Depression (HAM-D).

Review: Non-pharmacological interventions for depression in adults and children with traumatic brain injury

Comparison: 3 Transcranial magnetic stimulation plus TCA versus TCA alone

Outcome: 1 Hamilton Rating Scale for Depression (HAM-D)

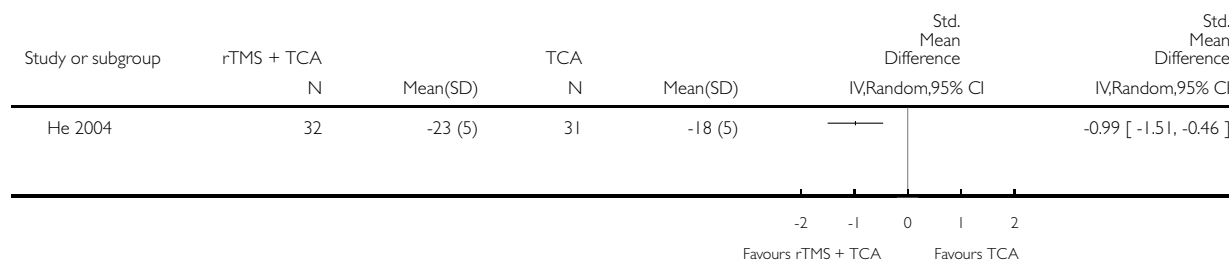


### Analysis 3.2. Comparison 3 Transcranial magnetic stimulation plus TCA versus TCA alone, Outcome 2 Mini Mental State Examination (MMSE).

Review: Non-pharmacological interventions for depression in adults and children with traumatic brain injury

Comparison: 3 Transcranial magnetic stimulation plus TCA versus TCA alone

Outcome: 2 Mini Mental State Examination (MMSE)

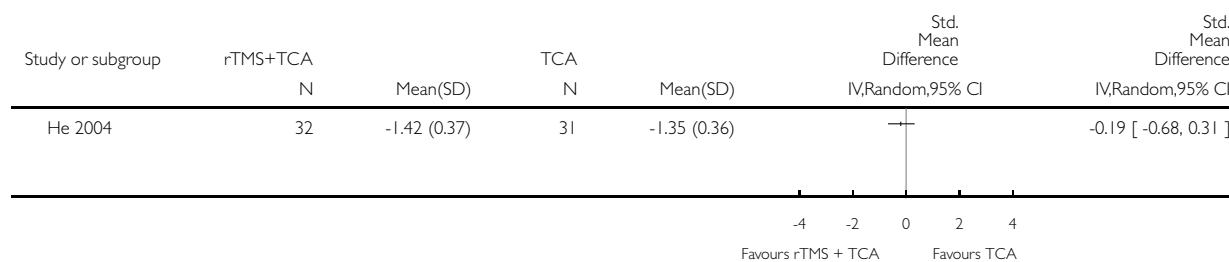


### Analysis 3.3. Comparison 3 Transcranial magnetic stimulation plus TCA versus TCA alone, Outcome 3 Serotonin (5-HT) levels.

Review: Non-pharmacological interventions for depression in adults and children with traumatic brain injury

Comparison: 3 Transcranial magnetic stimulation plus TCA versus TCA alone

Outcome: 3 Serotonin (5-HT) levels

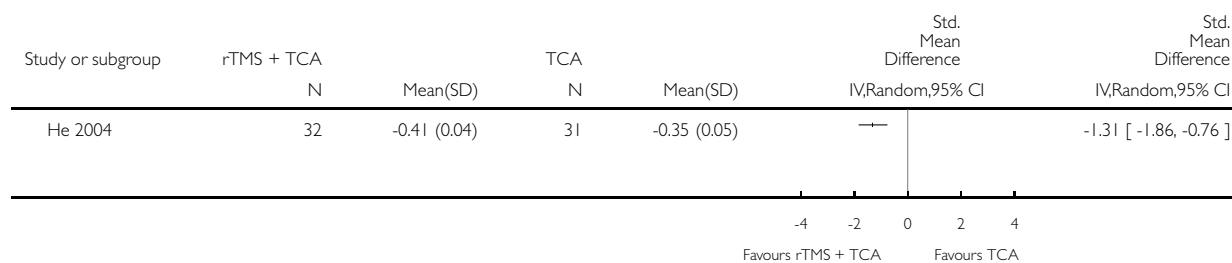


### Analysis 3.4. Comparison 3 Transcranial magnetic stimulation plus TCA versus TCA alone, Outcome 4 Noradrenaline.

Review: Non-pharmacological interventions for depression in adults and children with traumatic brain injury

Comparison: 3 Transcranial magnetic stimulation plus TCA versus TCA alone

Outcome: 4 Noradrenaline

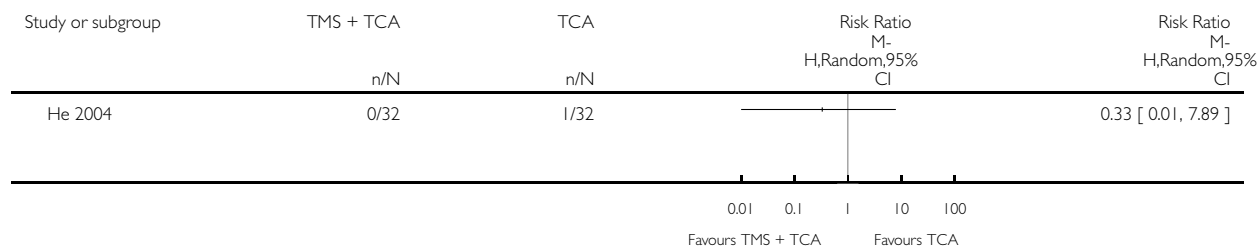


### Analysis 3.5. Comparison 3 Transcranial magnetic stimulation plus TCA versus TCA alone, Outcome 5 Treatment dropouts.

Review: Non-pharmacological interventions for depression in adults and children with traumatic brain injury

Comparison: 3 Transcranial magnetic stimulation plus TCA versus TCA alone

Outcome: 5 Treatment dropouts

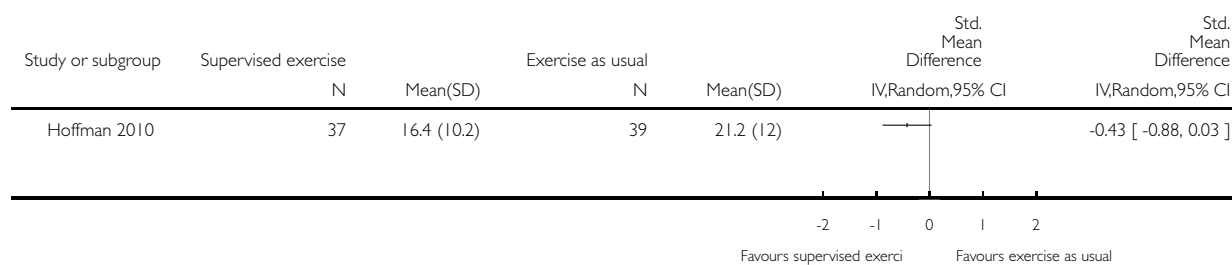


### Analysis 4.1. Comparison 4 Supervised exercise versus exercise as usual, Outcome 1 Beck Depression Inventory (BDI).

Review: Non-pharmacological interventions for depression in adults and children with traumatic brain injury

Comparison: 4 Supervised exercise versus exercise as usual

Outcome: 1 Beck Depression Inventory (BDI)

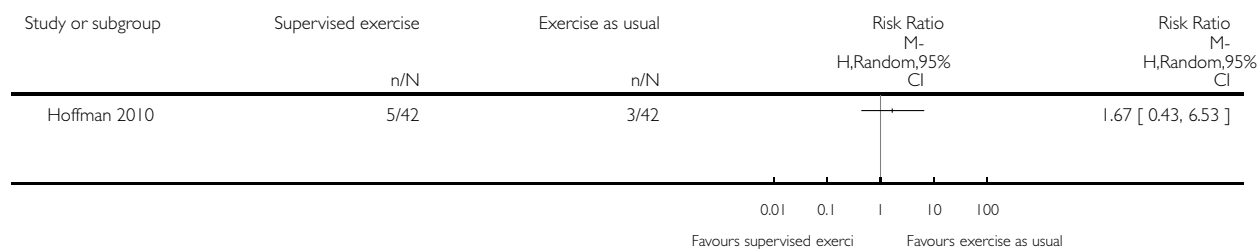


### Analysis 4.2. Comparison 4 Supervised exercise versus exercise as usual, Outcome 2 Treatment dropouts.

Review: Non-pharmacological interventions for depression in adults and children with traumatic brain injury

Comparison: 4 Supervised exercise versus exercise as usual

Outcome: 2 Treatment dropouts



## APPENDICES

### Appendix I. Search strategies

At the time of running the search we could not access **PsycBITE** and for that reason we ran only one search in this database in 2012.

#### **Cochrane Injuries Group Specialised Register**

(TBI OR "Traumatic Brain Injury") AND (depress\* OR dysthmic\*)

#### **Database of Abstract of Reviews of Effects (DARE) (The Cochrane Library)**

#### **Cochrane Central Register of Controlled Trials (CENTRAL, The Cochrane Library)**

#1MeSH descriptor Craniocerebral Trauma explode all trees

#2MeSH descriptor Brain Edema explode all trees

#3MeSH descriptor Glasgow Coma Scale explode all trees

#4MeSH descriptor Glasgow Outcome Scale explode all trees

#5MeSH descriptor Unconsciousness explode all trees

#6MeSH descriptor Cerebrovascular Trauma explode all trees

#7MeSH descriptor Pneumocephalus explode all trees

#8MeSH descriptor Cerebral Hemorrhage, Traumatic explode all trees

#9((head or crani\* or cerebr\* or capitis or brain\* or forebrain\* or skull\* or hemispher\* or intra?cran\* or inter?cran\* or intracran\* or intercran\*) NEAR/3 (injur\* or trauma\* or damag\* or lesion\* or wound\* or destruction\* or oedema\* or edema\* or contusion\* or concus\* or fracture\*))

#10((head or crani\* or cerebr\* or brain\* or intra?cran\* or inter?cran\* or intracran\* or intercran\*) NEAR/3 (haematoma\* or hematoma\* or haemorrhag\* or hemorrhag\* or bleed\* or pressur\*))

#11(Glasgow NEXT (coma or outcome) NEXT (scale\* or score\*))

#12"rancho los amigos scale"

#13("diffuse axonal injury" or "diffuse axonal injuries")

#14((brain or cerebral or intracranial) NEAR/3 (oedema or edema or swell\*))

#15((unconscious\* or coma\* or concuss\* or 'persistent vegetative state') NEAR/3 (injur\* or trauma\* or damag\* or wound\* or fracture\* or contusion\* or haematoma\* or hematoma\* or haemorrhag\* or hemorrhag\* or pressur\*))

#16MeSH descriptor Coma explode all trees

#17(injur\* or trauma\* or damag\* or wound\* or fractur\* or contusion\* or haematoma\* or hematoma\* or haemorrhag\* or hemorrhag\* or pressur\* or lesion\* or destruction\* or oedema\* or edema\* or contusion\* or concus\*)

#18(#16 AND #17)

#19(#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #18)

#20MeSH descriptor Depression, this term only

#21MeSH descriptor Depressive Disorder, this term only

#22MeSH descriptor Depressive Disorder, Major, this term only

#23MeSH descriptor Dysthymic Disorder, this term only

#24(depress\* or melancholia)

#25(#20 OR #21 OR #22 OR #23 OR #24)

#26(#19 AND #25)

#### **MEDLINE (OvidSP)**

1. exp Craniocerebral Trauma/

2. exp Brain Edema/

3. exp Glasgow Coma Scale/

4. exp Glasgow Outcome Scale/

5. exp Unconsciousness/

6. exp Cerebrovascular Trauma/

7. exp Pneumocephalus/

8. exp Epilepsy, post traumatic/

9. exp Cerebral hemorrhage, traumatic/

10. ((head or crani\* or cerebr\* or capitis or brain\* or forebrain\* or skull\* or hemispher\* or intra?cran\* or inter?cran\* or intracran\* or intercran\*) adj3 (injur\* or trauma\* or damag\* or lesion\* or wound\* or destruction\* or oedema\* or edema\* or contusion\* or concus\* or fracture\*)).ab,ti.
11. ((head or crani\* or cerebr\* or brain\* or intra?cran\* or inter?cran\* or intracran\* or intercran\*) adj3 (haematoma\* or hematoma\* or haemorrhag\* or hemorrhag\* or bleed\* or pressur\*)).ti,ab.
12. (Glasgow adj (coma or outcome) adj (scale\* or score\*)).ab,ti.
13. "rancho los amigos scale".ti,ab.
14. ("diffuse axonal injury" or "diffuse axonal injuries").ti,ab.
15. ((brain or cerebral or intracranial) adj3 (oedema or edema or swell\*)).ab,ti.
16. ((unconscious\* or coma\* or concuss\* or 'persistent vegetative state') adj3 (injur\* or trauma\* or damag\* or wound\* or fracture\* or contusion\* or haematoma\* or hematoma\* or haemorrhag\* or hemorrhag\* or pressur\*)).ti,ab.
17. exp coma/
18. (injur\* or trauma\* or damag\* or wound\* or fractur\* or contusion\* or haematoma\* or hematoma\* or haemorrhag\* or hemorrhag\* or pressur\* or lesion\* or destruction\* or oedema\* or edema\* or contusion\* or concus\*).ti,ab.
19. 17 and 18
20. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 19
21. randomi?ed.ab,ti.
22. randomized controlled trial.pt.
23. controlled clinical trial.pt.
24. placebo.ab.
25. clinical trials as topic.sh.
26. randomly.ab.
27. trial.ti.
28. 21 or 22 or 23 or 24 or 25 or 26 or 27
29. (animals not (humans and animals)).sh.
30. 28 not 29
31. (rat\* or rodent\* or mouse or mice or murin\* or dog\* or canine\* or cat\* or feline\* or rabbit\* or pig\* or porcine or swine or sheep or ovine\* or guinea pig\* or horse\* or hamster\* or goat\* or chick or cattle or bovine).ti.
32. 30 not 31
33. 20 and 32
34. Depression/
35. depressive disorder/ or depressive disorder, major/ or dysthymic disorder/
36. (depress\* or melancholia).ab,ti.
37. 34 or 35 or 36
38. 33 and 37

### Embase (OvidSP)

1. exp head injury/
2. exp brain edema/
3. exp Glasgow coma scale/
4. exp Glasgow outcome scale/
5. exp unconsciousness/
6. exp cerebrovascular accident/
7. exp pneumocephalus/
8. exp traumatic epilepsy/
9. exp brain hemorrhage/
10. ((head or crani\* or cerebr\* or capitis or brain\* or forebrain\* or skull\* or hemispher\* or intra?cran\* or inter?cran\* or intracran\* or intercran\*) adj3 (injur\* or trauma\* or damag\* or lesion\* or wound\* or destruction\* or oedema\* or edema\* or contusion\* or concus\* or fracture\*)).ab,ti.
11. ((head or crani\* or cerebr\* or brain\* or intra?cran\* or inter?cran\* or intracran\* or intercran\*) adj3 (haematoma\* or hematoma\* or haemorrhag\* or hemorrhag\* or bleed\* or pressur\*)).ti,ab.
12. (Glasgow adj (coma or outcome) adj (scale\* or score\*)).ab,ti.
13. "rancho los amigos scale".ti,ab.

14. (“diffuse axonal injury” or “diffuse axonal injuries”).ti,ab.
15. ((brain or cerebral or intracranial) adj3 (oedema or edema or swell\*)).ab,ti.
16. ((unconscious\* or coma\* or concuss\* or 'persistent vegetative state') adj3 (injur\* or trauma\* or damag\* or wound\* or fracture\* or contusion\* or haematoma\* or hematoma\* or haemorrhag\* or hemorrhag\* or pressur\*)).ti,ab.
17. exp coma/
18. (injur\* or trauma\* or damag\* or wound\* or fractur\* or contusion\* or haematoma\* or hematoma\* or haemorrhag\* or hemorrhag\* or pressur\* or lesion\* or destruction\* or oedema\* or edema\* or contusion\* or concus\*).ti,ab.
19. 17 and 18
20. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 19
21. exp Randomized Controlled Trial/
22. exp controlled clinical trial/
23. randomi?ed.ab,ti.
24. placebo.ab.
25. \*Clinical Trial/
26. randomly.ab.
27. trial.ti.
28. 21 or 22 or 23 or 24 or 25 or 26 or 27
29. exp animal/ not (exp human/ and exp animal/)
30. 28 not 29
31. (rat\* or rodent\* or mouse or mice or murin\* or dog\* or canine\* or cat\* or feline\* or rabbit\* or pig\* or porcine or swine or sheep or ovine\* or guinea pig\* or horse\* or hamster\* or goat\* or chick or cattle or bovine).ti.
32. 30 not 31
33. 20 and 32
34. Depression/
35. depressive disorder/ or depressive disorder, major/ or dysthymic disorder/
36. (depress\* or melancholia).ab,ti.
37. 34 or 35 or 36
38. 33 and 37

### **CINAHL Plus (EBSCO)**

- S1 (MH “Clinical Trials”)
- S2 PT clinical trial\*
- S3 TX clinical N3 trial\*
- S4 TI ( (singl\* N3 blind\*) or (doubl\* N3 blind\*) or (trebl\* N3 blind\*) or (tripl\* N3 blind\*) ) or TI ( (singl\* N3 mask\*) or (doubl\* N3 mask\*) or (trebl\* N3 mask\*) or (tripl\* N3 mask\*) ) or AB ( (singl\* N3 blind\*) or (doubl\* N3 blind\*) or (trebl\* N3 blind\*) ) or AB ( (singl\* N3 mask\*) or (doubl\* N3 mask\*) or (trebl\* N3 mask\*) or (tripl\* N3 mask\*) )
- S5 TX randomi?ed N3 control\* N3 trial\*
- S6 (MH “Placebos”)
- S7 TX placebo\*
- S8 (MH “Random Assignment”)
- S9 TX random\* N3 allocat\*
- S10 MH quantitative studies
- S11 S1 or S2 or S3 or S4 or S5 or S6 or S7 or S8 or S9 or S10
- S12 (MH “Head Injuries+”)
- S13 (MH “Cerebral Edema+”)
- S14 (MH “Glasgow Coma Scale”)
- S15 (MH “Unconsciousness+”)
- S16 (MH “Pneumocephalus”)
- S17 (MH “Epilepsy, Post-Traumatic”)
- S18 (MH “Cerebral Hemorrhage+”)
- S19 (head or crani\* or cerebr\* or capitis or brain\* or forebrain\* or skull\* or hemispher\* or intra?cran\* or inter?cran\* or intracran\* or intercran\*)
- S20 (injur\* or trauma\* or damag\* or lesion\* or wound\* or destruction\* or oedema\* or edema\* or contusion\* or concus\* or fracture\*)

S21 S19 N3 S20  
 S22 (head or crani\* or cerebr\* or brain\* or intra?cran\* or inter?cran\* or intracran\* or intercran\*)  
 S23 (haematoma\* or hematoma\* or haemorrhag\* or hemorrhag\* or bleed\* or pressur\*)  
 S24 S22 N3 S23  
 S25 “glasgow coma scale”  
 S26 “glasgow outcome scale”  
 S27 “rancho los amigos scale”  
 S28 “diffuse axonal injury” or “diffuse axonal injuries”  
 S29 (brain or cerebral or intracranial)  
 S30 (oedema or edema or swell\*)  
 S31 S29 N3 S30  
 S32 (unconscious\* or coma\* or concuss\* or 'persistent vegetative state')  
 S33 (injur\* or trauma\* or damag\* or wound\* or fracture\* or contusion\* or haematoma\* or hematoma\* or haemorrhag\* or hemorrhag\* or pressur\*)  
 S34 S32 N3 S33  
 S35 (MH “Coma”)  
 S36 (injur\* or trauma\* or damag\* or wound\* or fractur\* or contusion\* or haematoma\* or hematoma\* or haemorrhag\* or hemorrhag\* or pressur\* or lesion\* or destruction\* or oedema\* or edema\* or contusion\* or concus\*)  
 S37 S12 or S13 or S14 or S15 or S16 or S17 or S18 or S21 or S24 or S25 or S26 or S27 or S28 or S31 or S34 or S35 or S36  
 S38 (MH “Depression”)  
 S39 depress\* or melancholia  
 S40 (MH “Dysthymic Disorder”)  
 S41 “major depressive disorder”  
 S42 S38 or S39 or S40 or S41  
 S43 S11 and S37  
 S44 S42 and S43 Limiters - Exclude MEDLINE records

### PsycINFO (OvidSP)

1. exp Brain Damage/
2. exp Traumatic Brain Injury/
3. exp Epilepsy/
4. exp Cerebral Hemorrhage/
5. ((head or crani\* or cerebr\* or capitis or brain\* or forebrain\* or skull\* or hemispher\* or intra?cran\* or inter?cran\* or intracran\* or intercran\*) adj3 (injur\* or trauma\* or damag\* or lesion\* or wound\* or destruction\* or oedema\* or edema\* or contusion\* or concus\* or fracture\*)).ab,ti.
6. ((head or crani\* or cerebr\* or brain\* or intra?cran\* or inter?cran\* or intracran\* or intercran\*) adj3 (haematoma\* or hematoma\* or haemorrhag\* or hemorrhag\* or bleed\* or pressur\*)).ti,ab.
7. (Glasgow adj (coma or outcome) adj (scale\* or score\*)).ab,ti.
8. “rancho los amigos scale”.ti,ab.
9. (“diffuse axonal injury” or “diffuse axonal injuries”).ti,ab.
10. ((brain or cerebral or intracranial) adj3 (oedema or edema or swell\*)).ab,ti.
11. ((unconscious\* or coma\* or concuss\* or 'persistent vegetative state') adj3 (injur\* or trauma\* or damag\* or wound\* or fracture\* or contusion\* or haematoma\* or hematoma\* or haemorrhag\* or hemorrhag\* or pressur\*)).ti,ab.
12. exp Coma/
13. (injur\* or trauma\* or damag\* or wound\* or fractur\* or contusion\* or haematoma\* or hematoma\* or haemorrhag\* or hemorrhag\* or pressur\* or lesion\* or destruction\* or oedema\* or edema\* or contusion\* or concus\*).ti,ab.
14. 12 and 13
15. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 14
16. Depression/
17. depressive disorder/ or depressive disorder, major/ or dysthymic disorder/
18. (depress\* or melancholia).ab,ti.
19. 16 or 17 or 18
20. 15 and 19



21. exp clinical trials/
22. exp placebo/
23. exp treatment effectiveness evaluation/
24. exp mental health program evaluation/
25. exp experimental design/
26. exp prospective studies/
27. clinical trial\*.ab,ti.
28. controlled clinical trial.ab,ti.
29. randomi?ed controlled trial.ab,ti.
30. randomi?ed.ab,ti.
31. placebo.ab.
32. randomly.ab.
33. trial.ti.
34. ((singl\* or doubl\* or trebl\* or tripl\*) adj3 (blind\* or dummy or mask\*)).ab,ti.
35. ((crossover or clin\* or control\* or compar\* or evaluat\* or prospectiv\*) adj3 (trial\* or studi\* or study)).ab,ti.
36. 21 or 22 or 23 or 24 or 25 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35
37. exp animals/
38. exp human females/
39. exp human males/
40. 38 or 39
41. 37 not (37 and 40)
42. 36 not 41
43. 20 and 42

#### **PsycBite (OvidSP)**

depression AND "Traumatic Brain Injury"/Head Injury

## **CONTRIBUTIONS OF AUTHORS**

Paul Gertler: developed the concepts for the review, created the protocol with the assistance of the co-authors, undertook and coordinated all aspects of the systematic review and authored the final publication.

Robyn Tate: provided guidance and support in the conceptualisation of the review, provided assistance and editing in writing the protocol, culled abstracts and rated the methodological quality of the selected studies, and assisted with completion of the final publication.

Ian Cameron: provided assistance in the development of the protocol, guidance during the search process and editing advice on the final publication.

## **DECLARATIONS OF INTEREST**

PG: None known.

RT: None known.

IC: None known.

## SOURCES OF SUPPORT

### Internal sources

- Rehabilitation Studies Unit, Northern Clinical School, Sydney Medical School, The University of Sydney, Australia. Infrastructure and support services

### External sources

- Australian Cochrane Centre, Australia. Provision of introductory training and review completion workshops. Advice from Cochrane trainers and assistance in translation of an included study.
- Cochrane Injuries Group, UK. Provision of advice regarding trial registration. Assistance with design of the review protocol. Provision of search string for MEDLINE and translation for use in other databases. Provision of database search results abstracts and assistance locating studies that were not available online or in local libraries. Guidance during the study search phase of the review. Assistance in locating local training resources.

## DIFFERENCES BETWEEN PROTOCOL AND REVIEW

Search for studies: proceedings of the World Congress of Behavioral and Cognitive Therapies was not available.

Methods, Types of participants: *“Where possible, the review will include tables providing categorisation by depressive conditions or symptom severity and stratification of studies by age group (child 0 to 12 years, adolescent 13 to 17 years, adult 18 to 64 years, and older adults 65 years or more).”* This was not possible because the studies identified only included adults.

## **CHAPTER 2**

### **Section 2**

*Addendum to the Cochrane systematic review*

The publication of Gertler, Tate, and Cameron (2015) Cochrane systematic review was the culmination of a process that began with the registration of the review title with the Cochrane Collaboration in 2011 and subsequent publication of the mandatory review protocol in the Cochrane Library (Gertler, Tate, & Cameron, 2012). The study search was originally conducted in 2012 but completion of the review was held over until the publication of three studies that had been identified as ‘in progress.’ The final study search was conducted in February 2015 and the review was published in December 2015. Since that time, the authors are aware of four additional studies which would fulfil criteria for inclusion in an update of the Cochrane systematic review. These are briefly described below.

### 2.2.1 Repetitive Transcranial Magnetic Stimulation

Hoy et al. (2019) conducted a trial of repetitive transcranial magnetic stimulation (rTMS) in which rTMS was compared with a meaningful “sham” control condition. In the sham condition the rTMS equipment was put on participants and switched on but was directed away from participants so that stimulation could not be delivered. Hoy et al. found a statistically significant reduction in the Montgomery Asberg Depression Rating Scale across all participants (effect size  $d=0.21$ ) over the four-week trial but did not find a significant effect of rTMS over the control condition. This is a useful replication of the He, Yu, Yang, and Yang (2004) study. It was limited by small sample size ( $n = 21$ ) including attrition of three participants who were analysed as part of the intention-to-treat data analytic protocol. Hoy et al. did find some effects on cognitive measures but opined that these could have been practice effects. They posited that rTMS could have been effective if delivered at higher dosages and commented that recent studies recommend higher stimulation levels.

Considering that they did not find any adverse effects they suggested it would be possible to replicate the study with higher dosages of rTMS.

### 2.2.2 Windows to Hope: Replication

Brenner et al. (2018) conducted a replication of the previous Simpson, Tate, Whiting, and Cotter (2011) evaluation of the “Windows to Hope” program but with a US Military Veteran sample. The first study used the HADS-Depression and Brenner used the Beck Depression Inventory (BDI). Both studies targeted hopelessness and suicidality with a treatment group (n=15) receiving the “Windows to Hope” CBT program compared to a waitlist control group (n=20). Brenner et al. found significant reductions in the primary outcome measure of hopelessness but no group effect for the BDI and this was thought to be due to a significant difference between groups on the BDI at baseline and reductions in both groups over time.

### 2.2.3 Adapted CBT with motivational interviewing and booster sessions

Ponsford et al. (2016) conducted an evaluation of CBT adapted to TBI compared with waitlist control. The sample included 75 people with TBI who were diagnosed with depression and/or anxiety. One key difference, compared with other CBT studies included in the Cochrane review, was that Ponsford et al. investigated the effect of three sessions of Motivational Interviewing (MI) as a preparatory intervention versus three sessions of Non-Directive Counselling (NDC). There was no effect of MI versus NDC. Ponsford et al. also evaluated the effect of three booster sessions between 21- and 30-weeks post-recruitment. There was a significant improvement in HADS-Depression (effect size  $g=0.68$ ) and DASS-Depression (effect size  $g=0.82$ ) scores at 30 weeks compared with waitlist, which was not apparent at 21 weeks. Therefore, the authors concluded that additional booster sessions

had led to a significant benefit over the standard-length CBT programme. An additional factor in this study is that it sought to treat depression and anxiety symptoms concurrently which was beyond the scope of other studies so far identified. In personal communication one of the study authors (D. Wong, January 28, 2020) suggested that treating anxiety potentially led to an increase in engagement in potentially enjoyable and satisfying activities, and this might have led to an improvement in depression symptoms.

#### 2.2.4 Acceptance and Commitment Therapy for Adjustment to TBI (ACT-Adjust)

Whiting, Deane, McLeod, Ciarrochi, and Simpson (2019) conducted a pilot RCT of an Acceptance and Commitment Therapy intervention for psychological adjustment following TBI that they termed “ACT-Adjust”. This study would be included in an updated Cochrane review by virtue of criteria that specify the inclusion of participants with TBI who score above a clinical cut-off score on a depression scale (DASS21-Depression > 13). Participants were randomised to either the seven session ACT-Adjust program (n=10) or an active control Befriending therapy. Participants in the ACT-Adjust program demonstrated statistically significant improvements in DASS21-depression with the group moving from moderate-severe at baseline to mild-moderate following treatment (effect size Partial  $\eta^2=0.24$ ). This level was maintained at one-month follow up. The Befriending therapy control group remained in the moderate-severe range.

### **Conclusions**

These four studies represent important developments in the literature pertaining to interventions for depression after TBI. The studies showed positive outcomes for ACT-Adjust

and CBT but not for rTMS. A further study showed benefits of CBT for suicidality and hopelessness but not depression per se.

The Cochrane review included meta-analysis with three studies of CBT-based interventions versus a control condition. This found a very small effect in favour of CBT albeit with a very wide confidence interval such that the review could not recommend CBT. Integrating Ponsford et al. (2016) into the meta-analysis would not change these findings. Although the results at 30-weeks did demonstrate the benefit of an extended CBT-based intervention, this was after three additional booster sessions. These results could not be included in the meta-analyses because this only considered results immediately after a standard course of treatment (not including booster sessions). One study (Fann et al., 2015) did provide data for 8-week follow up but did not provide any treatment during the follow-up period, therefore the long-term results of Ponsford et al. need to be considered separately. Regardless of this, it is likely that an update of the Cochrane review would recommend a course of CBT plus additional booster sessions for clinical use.

Similarly, is unlikely that Whiting et al. (2019) could be included in the meta-analysis of CBT versus control conditions. Although there are components of ACT that are similar to CBT, the intervention is appreciably distinct and adopts a very different approach to handling unhelpful thoughts and emotions. Nevertheless, Whiting et al. demonstrated the benefit of ACT-Adjust and it is likely that an updated Cochrane review would recommend this intervention.

The Brenner et al. (2018) study is unlikely to change the recommendations of an updated Cochrane review, because it effectively replicated the findings of Simpson et al. (2011) which was already included in the CBT versus control condition meta-analysis. However, it does strengthen the earlier findings that “Windows to Hope” is beneficial for TBI patients who are suicidal and/or demonstrate a great deal of hopelessness.

Finally, Hoy et al. (2019) might change the conclusions of the Cochrane review because it provides more data from a higher quality study of rTMS that could be combined into a meta-analysis with He et al. (2004), which had positive findings for rTMS but had a high risk of bias.

In conclusion, it has been four years since the Cochrane review and further eligible empirical studies have been published in the interim that might change the conclusions of the review. It is probably timely to embark on a formal update of the systematic review for publication in the Cochrane library. This will be a substantial undertaking that will require a new search of databases, conference proceedings, key journals and grey literature from February 2015, further data extraction and analysis and evaluation of the methodological quality of newly identified studies. The authors intend to conduct a formal update of the Cochrane review over the coming years.

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<sup>1</sup> Note: DOI is linked to the full (2015) review. The protocol text is included in the final review document and any deviation from the protocol is discussed in the review.

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## CHAPTER 3

### ***Making sense of data analytic techniques used in a Cochrane systematic review***

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Cochrane systematic review. *Brain Impairment*, 19(1), 81-90.

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# Making Sense of Data Analytic Techniques used in a Cochrane Systematic Review

Between-groups research

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Systematic reviews have developed over the past 40 years as a method for integrating findings from the available studies relating to clinical problems and interventions into one publication. Systematic reviews employ a variety of data analytic techniques including meta-analysis, which combines treatment effects across disparate studies in order to produce a truer estimate of treatment effect. The Cochrane Collaboration was established in order to facilitate access to high-quality evidence and specifies stringent guidelines for the production of systematic reviews. A Cochrane Systematic Review (CSR) includes consideration of the risk-of-bias of the selected studies in reaching conclusions. A recent CSR is used as an example to demonstrate the process of conducting a CSR, the data analytic methods employed and the assumptions made when employing these methods. There is a discussion of issues the reader will need to be aware of when considering the findings of a CSR and how this might differ from other systematic reviews including some consideration of how CSRs apply to the brain impairment literature.

**Keywords:** Systematic review, Cochrane review, Meta-analysis, Research Methodology, Data analysis, Data analytic techniques, Rehabilitation outcomes, Treatment outcomes, Evidence-based medicine, Neurorehabilitation, Acquired Brain Injury, Traumatic Brain Injury

## Introduction

Systematic reviews attempt to summarise available research on a topic in a way that is methodical and informative to researchers, practitioners and other decision makers. Cochrane systematic reviews (CSRs) set out to provide the highest quality systematic review which, in turn, produces the most reliable findings. This article discusses systematic reviews and the data analytic techniques that are employed, foremost amongst these is meta-analysis, as demonstrated by reference to a recently conducted CSR relating to a brain impairment population.

## *Historical Context of the Cochrane Systematic Review*

The Cochrane Collaboration began with the opening of the first Cochrane Centre in Oxford, UK and subsequently the first Cochrane Colloquium in the early 1990s. The leading force behind the Cochrane Collaboration was Sir Iain Chalmers, an obstetrician and gynaecologist who has dedicated much of his career to the promotion of evidence-based medicine. Chalmers came to realise that some of the interventions that he had been trained to deliver did more harm than good and resulted in prolonged suffering and

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unnecessary deaths (Hawkes, 2014). Chalmers questioned the evidence for common interventions. He was influenced by Archie Cochrane's work in the 1970s which called for the promotion of the randomised controlled trial (RCT) and the registering and reporting of all RCTs of an intervention or clinical problem in order to best inform medical practice (The Cochrane Collaboration, 2013).

The hallmarks of the Cochrane Collaboration are:

1. Reviews are usually based on RCTs in order to reduce the possibility of biases influencing research outcomes.
2. All the available RCTs and quasi-RCTs on a particular subject are catalogued into one central database known as CENTRAL.
3. There is recognition that not all studies are published but will still have important findings which impact on the conclusions that can be drawn about a particular treatment. Therefore, it is important to search exhaustively for any research relevant to the topic. This includes a Grey Literature search. Grey Literature relates to research activity which is not necessarily available in standard publications. It might be found in registries of trials, the proceedings of funding bodies and other sources that are not formally published. GreyNet International ([www.greynet.org](http://www.greynet.org)) provides an avenue to search for Grey Literature or alternatively authors of systematic reviews need to identify likely sources of Grey Literature (e.g., funding announcements).
4. Information is critically evaluated and is in a format accessible to clinicians, researchers and also consumers of interventions.
5. The Cochrane Collaboration promotes the inclusion of research findings, and encourages collaborations of researchers, from all over the world. The search is not limited to any particular language.
6. CSRs are published electronically in order to provide the most current and accessible reviews.
7. The Cochrane Collaboration relies mainly on unpaid work to compile the reviews.
8. CSRs use of a variety of statistical techniques in order to analyse data yielded by the reviews. Where multiple sources of data exist, this introduces the possibility of using meta-analysis to better understand the available studies and the effects of interventions.

### *Development of Meta-analytic Techniques*

In parallel to the invention of the systematic review, the 1970s saw the pioneering of meta-analysis as a data analytic technique for managing the data identified in a systematic review. The term 'meta-analysis' was first attributed to Gene Glass in 1976 (Shadish, 2015). Glass, working simultaneously with other researchers in psychology (Frank Schmidt and Robert Rosenthal), was interested in data analytic methods that would enable the synthesis of data from multiple studies across interventions or clinical problems. These researchers recognised that there was a need for the integration of research findings across studies which would take into account biases related to the methodological quality of the primary studies (Shadish & Lecy, 2015).

Glass defined meta-analysis as the analysis of summary statistics from studies rather than the analysis of raw data. In a discussion of the origins of meta-analysis, Glass (2015, p. 223) reflected on how he had used meta-analysis 'to do battle' against Hans Eysenck, whose 1965 review of the psychotherapy outcome literature had criticised the effectiveness of psychotherapy. When Glass inspected Eysenck's methodology he found several sources of biases and this inspired him to develop an objective data analytic method that would prove Eysenck's findings wrong.

From the 1970s, there was at first a trickle and then a flood of meta-analytic studies. It follows that with the advent of meta-analytic studies in the social sciences and the push towards evidence-based medicine from key figures such as Archie Cochrane, the conditions were set for the development of the systematic review as an influential research methodology and for the proliferation of the CSR. As of the 20th anniversary of the Cochrane Collaboration in 2013 there were more than 5,000 published CSRs and nearly 28,000 researchers across 120 countries had participated in the authoring of a CSR (The Cochrane Collaboration, 2013).

### *Systematic Reviews in the Field of Brain Impairment*

The brain impairment literature was greatly influenced by the publication of the first systematic review of cognitive rehabilitation by Keith Cicerone and colleagues in 2000 (Cicerone et al., 2000). While it was limited in its sources, using only one database (Medline), it did yield 171 studies which ranged in levels of evidence from 'class 1' trials of RCTs through to 'class 3' case reports or case series. Cicerone formed a panel of experts who reviewed the literature systematically resulting in

recommendations for clinical practice across three grades of evidence. This group subsequently published updates in order to provide more current information (Cicerone et al., 2005; 2011). A subsequent meta-analysis of this data by Rohling, Faust, Beverly and Demakis (2009) showed a small effect in favour of some interventions for TBI and stroke patients.

The development of the systematic review occurred in parallel with the shift towards evaluating evidence from RCTs and a growing skepticism in accepting results as published. This is seen today in the adoption of standards such as CONSORT (Consolidated Standards of Reporting Trial). Beginning in the 1990s (The Standards of Reporting Trials Group, 1994) and with updates since then, CONSORT set out to specify standards for the reporting of RCTs. When designing studies researchers can use the CONSORT guidelines to ensure that their study is of the highest possible methodological quality. Critically, there is a recognition within the CONSORT statement, that an RCT is a scientific experiment which needs to specify its design and methods *a priori* (Moher et al., 2010). There are also extensions to CONSORT for a range of designs (e.g., cluster or N-of-1 trials) and interventions (e.g., non-pharmacological).

The need to integrate an array of research findings has led to the invention of topic- or discipline-specific databases. This includes simple collections of studies that can be a way in which proponents of particular therapeutic approaches establish a research tradition, such as the list of RCTs of Acceptance and Commitment Therapy (ACT) maintained on the website of the Association for Contextual Behavioural Science (Hayes, 2017). Two examples of specialist field-driven databases of studies are PEDro, the physiotherapy evidence database and PsycBITE, the psychological database for brain impairment treatment efficiency. These databases aim to provide researchers and clinicians with ready access to relevant research findings which are curated to include a reliable judgment on the quality of the evidence. These databases are distinguished from other collections by involving a collaboration of clinicians and researchers who undertake a quality rating of the available evidence which is then available in a searchable database with open access. There are also databases for interventions in speech pathology (speechBITE), occupational therapy (OTseeker) and across broader health care disciplines (e.g., The Joanna Briggs Institute, EBM Online – evidence-based medicine). These databases are important avenues for knowledge translation from researchers to practising clinicians and may influence policy decision making, such as the Centre for Reviews and Dissem-

ination (CRD) database which disseminates research to policy-makers in the UK National Health Service. The advantage of the online, collaborative style databases such as PsycBITE is that they are regularly updated and provide a more current knowledge base (Tate et al., 2006) although it can be difficult securing the continuing funding required to maintain these databases.

A search of PsycBITE shows 789 systematic reviews that have been published in the field of brain impairment (search conducted 1 September 2017). The depth and quality of these reviews does vary with some of them preliminary ‘scoping reviews’ to CSRs. A search of the Cochrane Database of Systematic Reviews (search conducted 1 September 2017) with the search term ‘Brain Impairment’ returns 1,125 CSRs, applicable to a wide range of neurological conditions treated with pharmacological and non-pharmacological. CSRs tend to be affected by a relatively low number of available studies partially because they tend to be limited to RCTs, which are difficult to conduct in this population. Reasons why include difficulty recruiting and maintaining sufficient samples and the problem that any treatment provided is just one factor influencing the behaviour, mood, cognition or participation of people with brain impairment in amongst a variety of lifestyle factors. As an example McDonald et al. (2008) undertook a social skills training program with TBI participants. There was substantial dropout during the baseline assessment phase, treatment and lengthy follow up phases. It was difficult to establish a meaningful control condition and at the conclusion of treatment it was unclear whether change on the key outcome variables was due to participation in the group or other factors (e.g., change in social circumstances).

## The Process of Conducting a Cochrane Systematic Review

Systematic reviews set out to summarise the evidence relevant to a specific clinical question using a transparent, *a priori* protocol-driven approach. Compared to a literature review, a systematic review has: clearly defined objectives; predefined eligibility criteria; explicit, reproducible methodology; systematic search of sources; assessment of the validity of included studies and systematic synthesis and presentation of findings (Lockwood, Sfetcu, & Oh, 2011). By comparison with other systematic reviews, CSRs tend towards higher levels of evidence by recommending the inclusion of only RCTs. As such they sacrifice inclusiveness of a variety of studies and methodologies in order to

produce more reliable findings. Ultimately, a CSR may have fewer studies to draw upon however the true size and direction of the treatment effect will be clearer because there is an integration not just of findings but also the methodological strength of the primary studies contributing to these findings. As an example, there are several non-CSRs of treatments for emotional problems following acquired brain injury that attempt to integrate various research methodologies or clinical problems by applying less stringent inclusion criteria. The compromise for less stringent inclusion criteria is greater heterogeneity of studies and therefore less definitive conclusions about the effectiveness of a particular intervention for a specific clinical problem (e.g., Alderfer, Arciniegas, & Silver, 2005; Fann, Hart, & Schomer, 2009; Waldron, Casserly, & O'Sullivan, 2013). The authors of these systematic reviews may argue that including a broader pool of studies increases the clinical relevance of the review.

The Cochrane Collaboration sets strict criteria for the process of undertaking a CSR. Primarily, this is a collaborative process which starts with registering a topic area and title with one of the interest groups of the Collaboration. This process highlights the involvement of the Cochrane Collaboration in the development of each CSR. This is important to ensure that there is no overlap between review topics and that the Collaboration has confidence that the research team will be able to complete the review. Once the title is accepted the stage of protocol development begins. The protocol sets out all of the methodology by which the review will be conducted.

A rigorously conducted systematic review will establish a set of inclusion/exclusion criteria to determine those studies most relevant to the research aims and will not vary from those criteria. These criteria will lead to a search output along a continuum with either a broad array of varied primary studies or, in a more selective review, a group of primary studies that are strictly focused on the study aims and are of greater methodological quality.

The Cochrane Collaboration's strict criteria include the *a priori* establishment of a protocol for the undertaking of the CSR. This comprises the stated rationale for doing the review, sets out the search method by which the review will be conducted and how the data will be extracted and analysed. Herein we discuss Gertler, Tate and Cameron's (2015) CSR of non-pharmacological interventions for depression following traumatic brain injury (TBI) in children and adults, henceforth referred to as GTC. This review received substantial support from the Cochrane Injuries Group and assistance from the Australasian Cochrane

Centre including workshops for the author on writing a protocol and completing the review.

The study search for GTC included an exhaustive search string of relevant electronic databases which yielded over 2,000 records which were then considered for inclusion by two authors. In keeping with Archie Cochrane's assertion that not all relevant studies are available from standard publications, more than 14,000 records were screened from other sources (journals and conferences that typically related to the review topic). Of these records, almost all were excluded leaving just three studies that met inclusion criteria. A grey literature search identified three upcoming studies and the publication of the CSR was delayed until data from these studies was available. This left a total of six studies meeting inclusion criteria. These studies were then subjected to analysis using the Cochrane 'Risk of bias' tool (Higgins & Green, 2011).

Risk of bias assessment refers to an analysis of the threat posed to the conclusions of the study by systematic sources of bias. The Cochrane 'Risk of Bias' (referred to as RoB) assessment includes seven evidence-based domains which are: the randomness of participant allocation to groups; the concealment of allocation to groups; blinding of participants and personnel; blinding of outcome assessment; incomplete outcome data; selective report of outcomes and other identified sources of systematic biases. Review authors provide a judgment of the presence of low, high or unclear RoB for each domain.

## Data Analytic Techniques used in a Cochrane Systematic Review

CSRs can include a variety of data analytic techniques. These can be categorised into analyses which tell us about the nature of individual primary studies, and techniques that combine data from primary studies in order to make a more reliable conclusion about a treatment question. Specifically, whether a treatment is effective and whether it can be recommended. Conclusions about the reported effectiveness of a treatment must be tempered with an initial analysis of the reliability of the primary study, from which the conclusions are drawn.

Each primary study identified for a CSR is subjected to standardisation of the measure of treatment effect thus producing an 'effect size' or a standardised mean of the effect of the intervention. This is done in order to allow easier comparison between studies and as a pre-cursor to meta-analysis. In GTC this was the standardised mean difference (SMD) and 95% confidence interval for continuous data, such as the results of a questionnaire.

SMD is the difference in mean outcome between groups (i.e., the difference between intervention and control), divided by the standard deviation of that outcome measure across all the participants in the study, both intervention and control participants (Higgins & Green, 2011) as per the formula below:

$$\text{SMD} = \frac{\text{Difference in mean outcome between the groups}}{\text{Standard deviation of outcome amongst participants}}$$

The SMD method assumes that the variation in standard deviation of outcomes reflects variation in the outcome measure. Therefore, SMD reduces the influence of different outcome measures being used across studies. This method is also known as Hedges' (adjusted) *g*. Figure 1 shows the reported mean and standard deviation of each study and what the SMD is once transformed including a 95% confidence interval. As can be seen the SMD varied between a moderate effect in favour of intervention for 'Bedard, 2013' to a slight effect against for 'Simpson, 2011'.

Likewise, there is an effect size measure for dichotomous outcomes which in GTC was the risk ratio (RR) method. The dichotomous outcome was diagnostic status. The authors were interested in whether participants had a diagnosis of depression prior to enrolment in the study and what was the rate of recovery from diagnosis in the intervention group compared to the control group, or the relative rate of recovery between two active treatments. 'Risk' refers to the likelihood of a particular outcome such as the likelihood that participants receiving an intervention will no longer fulfil the diagnostic criteria for depression. The RR is effectively the rate of recovery in the experimental (intervention) group divided by the rate of recovery in the control group (Higgins & Green, 2011).

### *Applying Meta-analysis to a Systematic Review*

The availability of studies for comparison will vary depending on the type of intervention and the target clinical problem. Brain impairment studies are relatively obscure and our research group has found relatively few studies when undertaking other CSRs (Lane-Brown & Tate, 2009; Soo & Tate, 2007). It can be difficult to undertake RCTs because of the intensive resources required and individual studies are often under-powered because of low numbers of participants and high dropout rates. Meta-analysis provides an opportunity to combine similar studies to boost numbers and statistical power. It might also be that different studies draw different conclusions about a treatment

effect and so combining the results in a meta-analysis might shed some light on these disagreements (Higgins & Green, 2011).

The first consideration when conducting a meta-analysis is to determine the homogeneity of the collection of studies or, conversely, to consider if heterogeneity of selected studies will preclude meta-analysis. Higgins and Green (2011) describe variation between studies to do with participants, interventions and outcomes as 'clinical diversity.' In GTC, six studies were selected for inclusion in the review. Four studies included an evaluation of a psychological therapy and the other two were evaluations of separate and distinct physical interventions. Because of the disparity in the modes of treatment (psychological vs. physical) not all studies could be included in the same meta-analysis. Four studies used psychological interventions and three of these were a comparison between a psychological treatment and a control condition, whereas the remaining study was a comparison between two psychological treatments. It was decided that a study which compared two potentially active treatments was both clinically and methodologically distinct. Therefore, only those three studies that compared a psychological treatment with a control condition could be meaningfully combined in a meta-analysis.

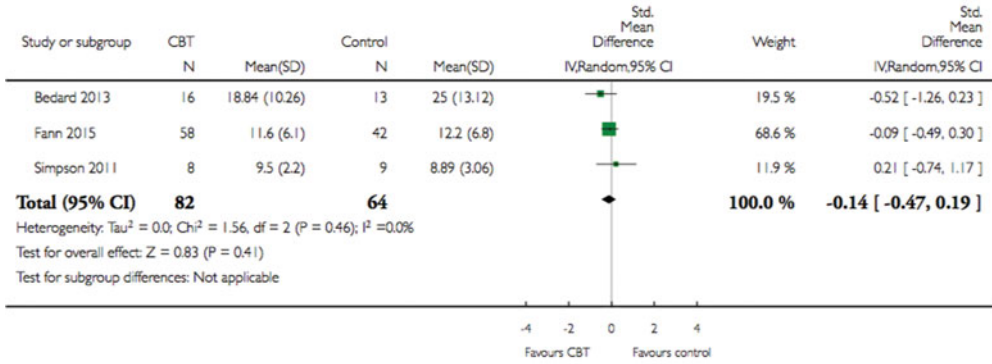
A further consideration was the appropriateness of the main outcome measure. In the topic area covered in GTC, there are two main categories of treatment outcome, either the participants' score on a symptom measure of depression, or the participants' diagnostic status (diagnosed or not diagnosed with a depressive condition). Of the three studies in consideration for meta-analysis all three used a score on a symptom questionnaire as a main outcome measure and had a similar design. Despite all three using different depression questionnaires as outcome measures it is possible to compare outcomes if we know some statistical information about the outcomes measures, i.e., the mean and standard deviation of the main outcomes. With growing awareness of standards such as CONSORT this information is usually reported however there are occasions where this information does not appear in a publication and it is necessary to search for this information or contact the study authors (e.g., Hoffman et al., 2010).

There is also statistical heterogeneity which may apply. Statistical heterogeneity may occur when there is very little or no overlap in the confidence interval of effect between the measures. Cochrane reviews include the Chi-squared statistic as a measure of heterogeneity. Chi-squared asks whether the observed differences between study outcomes are compatible with chance alone. The



**Analysis 1.3. Comparison 1 CBT versus control, Outcome 3 Depression scales.**

Review: Non-pharmacological interventions for depression in adults and children with traumatic brain injury  
 Comparison: 1 CBT versus control  
 Outcome: 3 Depression scales



**FIGURE 1**

Example of meta-analysis of three studies for one comparison in Gertler, Tate, and Cameron (2015).

threshold for significance is set at  $p < .10$  (Higgins & Green, 2011). The Chi-squared result is then further assessed using the  $I^2$  test of inconsistency which takes into account the degrees of freedom of the meta-analysis (how many studies are included). An  $I^2$  of below 30% indicates an unimportant level of inconsistency. Higher levels might indicate a level of inconsistency which would preclude meta-analysis (Higgins & Green, 2011). As can be seen in Figure 1 there was overlap in the forest plot of SMD and 95% confidence intervals in GTC.

Once we have established that we have a suite of comparable studies we can combine these in a meta-analysis. The Cochrane Collaboration makes this straightforward by including data analytic software in its proprietary Review Manager (RevMan) software package which is used to write the review.

Figure 1 above shows an example of a forest plot for a meta-analysis in GTC. This is a comparison of treatment vs. control or alternative treatment, just for one specific outcome measure, in this case it is for depression symptom scales. Figure 1 shows the SMD with 95% confidence interval for each study, which demonstrates the studies falling either side of an effect. It also shows the combined SMD with 95% confidence interval for the meta-analysis across the three studies, which shows a very slight effect in favour of CBT interventions (SMD = -0.14) but a 95% confidence interval that shows that CBT could be moderately effective

ranging to the control condition being mildly more effective.

Figure 1 indicates that the meta-analysis was conducted using the ‘inverse-variance’ (IV) method. Using the IV method studies that have greater variance are given lower weighting in the meta-analysis. The IV method thereby seeks to reduce the effect of studies with greater variance on the overall meta-analysis. The equation for this calculation is found in the Cochrane Handbook (Higgins & Green, 2011).

*Data Assumptions and what to Look for in Meta-analysis*

A notable feature of the GTC meta-analysis is that it uses a ‘random effects’ model as opposed to a ‘fixed effects’ model. In fixed-effects meta-analysis there is an assumption made that each study in the meta-analysis reflects the true effect of the intervention and that any variation between studies is solely due to chance. The fixed effects model asks, ‘what is the best estimate of the treatment effect?’ In a random effects analysis this assumption is not made but rather there is an assumption that each study follows a distribution of effect due to some source of heterogeneity across studies (Higgins & Green, 2011). This is usually a fair assumption to make when combining studies which use similar but not identical samples, modes and dosages of interventions and outcome

measures. The random effects model asks, 'what is the average intervention effect?' The random effects model comes with some potential pitfalls which are discussed below.

The calculation for SMD is the cornerstone of the meta-analysis. In a CSR, the SMD is first calculated for each study and this takes into account the variability of the outcome measure from that study's sample. If the study has a small number of participants, or a sample which is unusual in any way, then this would likely skew the findings. Cochrane attempts to minimise the impact of studies with high variability by assigning them less weight by recommending the IV method (the greater the variance the lower the weighting in the analysis). One of the key assumptions of meta-analysis is that study results which are pooled take into account the variance of each study when combined in the analysis and when this 'variability in variability' is not accounted for then this will lead to a less reliable conclusion. For example, Waldron, Casserly, and O'Sullivan (2013) merely averaged across the effect size estimate for each study to arrive at an average effect size from which positive conclusions were drawn about the effect of the intervention. The average effect size assumes that each study should be accorded equal weighting, despite the fact that some studies have a much greater variability in outcome than others. This is problematic because, as demonstrated by the wide 95% confidence interval in GTC, there can be highly variable outcomes ranging from moderate support for intervention to mild support for no intervention.

Even with the use of a 'random-effects' model, if the weighted average of the meta-analysis is given without context it might belie the heterogeneity of the studies included in the meta-analysis. The confidence interval is only an estimate around the mean and even with a small confidence interval this might not reflect the existence of outlier studies (Higgins & Green, 2011). To account for this RevMan includes a measure of 'tau-squared' which is an estimate of between study variance. This statistic is referred to in the output chart for GTC in Figure 1 along with other tests of inconsistency. An elevated tau-squared ( $\tau^2 > 1$ ) would indicate substantial heterogeneity which might indicate an invalid meta-analysis.

Readers should be aware, when considering the results of a meta-analysis, of the existence of other unreported sources of bias. One important risk of bias which is neglected in CSRs is the risk of bias represented by unequal groups at baseline. In meta-analysis, the relative effect and confidence interval is based on a comparison between groups following an intervention, however there are of-

ten studies in which the groups are not similar at baseline on the main outcome measures or significant demographic variables, for example, time since injury. If groups are not similar at baseline then it can be assumed that this would bias the response to intervention. This is a particular problem in small group studies where it is expected that differences in mean baseline score on outcome measures would be magnified. This is a source of systematic bias that could influence meta-analysis findings when there is a handful of studies included. While the Cochrane Collaboration has an accepted 'risk-of-bias' tool, this does not consider differences in baseline. By way of comparison the PEDro-P scale, as used by databases such as PEDro and PscBITE, includes an item that considers whether participants are equivalent at baseline on prognostic indicators and outcome measures.

One method for examining sources of bias, which is applicable to larger meta-analyses involving more than about 10 studies, is the use of a funnel plot. Sterne et al. (2011) defined a funnel plot as a scatter plot of effect estimates from individual studies against a measure of each study's size or precision as an indication of statistical power. The studies are then plotted along a vertical axis with the most powerful studies plotted at the top and the effect estimates from smaller studies scattered around the bottom of the plot. The effect estimates should congregate around a central line which is the weighted average effect produced by the meta-analysis. The resultant plot should resemble an inverted funnel. If no bias is present then a triangle centred on the fixed-effect estimate and extending 1.96 standard errors either side will include 95% of studies (Sterne et al., 2011). When the studies are plotted, the lack of a funnel shape, particularly on the side representing studies that demonstrate a lack of effectiveness, might indicate the presence of publication bias or another element of systematic bias.

Publication bias occurs when studies with contrary findings do not appear in the literature, presumably due to pressure to publish findings in support of an intervention. CSRs attempt to address publication bias by including a grey literature search and in GTC there was in fact the uncovering of relevant studies that had been logged in a trials registry but not completed. Sterne et al. (2011) provide options for a statistical test which might indicate a lack of funnel plot symmetry and discuss reasons why this might occur. It is important to question the existence of publication bias, especially considering that most researchers investigating a certain technique may be strong proponents of one particular approach or authors may strike opposition to reporting a null finding.

CBT compared to wait-list control for post-TBI depression						
Patient or population: Post-TBI depression Settings: Community setting Intervention: CBT Comparison: Wait-list control						
Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	wait-list control	CBT				
Depression scales (BDI-II, HAM-D and HADS); higher score means more depressed	The mean depression score in the control groups was 15.36 <sup>4</sup>	The mean depression score in the intervention groups was 0.14 standard deviation lower (0.47 lower to 0.19 higher)	SMD -0.14 (-0.47 to 0.19)	146 (3 RCTs)	⊕⊕⊕⊕ VERY LOW <sup>1,2,3</sup>	
*The basis for the assumed risk (e.g. the median control group risk across studies) is provided in footnotes. The corresponding risk (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI). CI: Confidence interval;						
GRADE Working Group grades of evidence High quality: Further research is very unlikely to change our confidence in the estimate of effect. Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate. Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate. Very low quality: We are very uncertain about the estimate.						
1 Of these three studies, there is variability in the quality of the evidence as it relates to risks of bias. <a href="#">Bedard 2013</a> had serious risk of bias as it related to random sequence generation (selection bias) and incomplete outcome data (attrition bias). <a href="#">Simpson 2011</a> suffered from other risks of bias due to a very small sample size. All three studies (including <a href="#">Fann 2015</a> ) were subject to biases that are virtually unavoidable when attempting an RCT on this topic. All studies suffered from lack of blinding as it relates to participants and personnel (performance bias) and blinding of outcome assessment (detection bias). 2 Small effect sizes. Two studies slightly favour CBT ( <a href="#">Bedard 2013</a> ; <a href="#">Fann 2015</a> ). One study slightly favours control ( <a href="#">Simpson 2011</a> ). 3 The 95% confidence interval of the outcome is very broad and ranges from a moderate effect in favour of CBT to a small effect against CBT. 4 The assumed risk was calculated by adding the means of the scores of the control groups and dividing by the number of studies in the analysis.						

**FIGURE 2**  
 GRADE Summary of Findings Table from Gertler, Tate, and Cameron (2015).

*GRADE Analysis*

The primary purpose of a systematic review is to collate all of the relevant research on a topic or intervention. If possible, the selected studies can be combined in a meta-analysis. CSRs go beyond this by excluding lower quality evidence (e.g., non-randomised group studies) and taking into account the quality of the identified studies in reaching conclusions and recommendations. This is demonstrated in a CSR by the use of ‘summary

of findings’ tables that include a GRADE analysis. GRADE is an acronym for Grades of Recommendation, Assessment, Development and Evaluation Working Group which comprised representatives from 20 global health organisations.

To conduct a GRADE analysis, authors of systematic review can access specialised GRADEPRO software via the GRADE website ([www.gradeworkinggroup.org](http://www.gradeworkinggroup.org)). As can be seen in [Figure 2](#), the GRADE analysis takes into account

the relative effect of the meta-analysis and integrates the quality of evidence which is derived from the risk of bias of each study. GRADE analyses also include a consideration of the risks of the intervention to the consumer. As can be seen from the screenshot of the main comparison in GTC the quality of the evidence is rated as 'very low'. The superscript endnotes indicate the reasons for this quality grade and in the case of GTC this was due to substantial differences in risk of biases between the selected studies, the small effect size and the very broad 95% confidence interval of the effect.

### Beyond Cochrane Reviews

Just as the quality of studies varies so does the quality of systematic reviews. This has led onto the development of 'systematic reviews of systematic reviews' which appraises available reviews on a topic and can guide decision making when there is contrasting evidence (Smith, Devane, Begley, & Clarke, 2011). Resulting from this is 'meta-analysis of meta-analyses' in which past meta-analyses may be re-analysed to form updated conclusions (Anker, Reinhart, & Feeley, 2010).

Finally, Cochrane and other systematic reviews are a primary source of evidence in the development of clinical practice guidelines such as the 'guidelines produced by the UK National Institute for Health and Clinical Excellence (NICE)'. Evidence from Cochrane and other systematic reviews may then have an influence on policy setting and the development of clinical services. The Cochrane Collaboration maintains a database of systematic reviews that have been quality assessed (referred to as 'DARE') and this can also be used by decision makers with questions about specific interventions when a CSR has not yet been undertaken.

### Concluding Comments

Systematic reviews developed as a way to integrate studies on a topic. Simultaneously, meta-analysis developed as a statistical method to combine treatment effects from various studies into an overall estimate of treatment effect. In keeping with the trend towards the production of higher-quality research, CSRs were developed as the gold-standard in systematic review. CSRs employ a variety of data-analytic techniques including meta-analysis. The quality of meta-analyses can vary and in a CSR weighting is given to studies based on statistical variability. Using a GRADE analysis, CSRs consider the results of the meta-analysis in the context of risk of biases in order to provide a reliable picture of treatment outcomes for a particular intervention or clinical problem. As such, CSRs pro-

vide useful guidance for clinicians, researchers, consumers and policy-makers.

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### Conflict of Interest

None.

### Ethical Standards

The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national and institutional committees on human experimentation and with the Helsinki Declaration of 1975, as revised in 2008.

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## CHAPTER 4

### ***Are single item mood scales (SIMS) valid for people with traumatic brain injury?***

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# Are single item mood scales (SIMS) valid for people with traumatic brain injury?

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## ABSTRACT

**Objectives:** Single-item mood scales (SIMS) are used in clinical practice and research as simple and convenient measures to track mood and response to interventions but have rarely been formally evaluated in neurological samples. The current study sought to evaluate the psychometric properties of SIMS in verbal and visual formats.

**Participants:** Sixty-one people living in community settings in metropolitan and regional Australia, with a history of traumatic brain injury.

**Methods:** SIMS were compared with measures of related constructs (depressed mood and satisfaction with life) on two occasions between one and three weeks apart.

**Results:** The study met COSMIN method quality criteria for evaluation of validity. The SIMS showed evidence of construct validity, having moderate magnitude correlation coefficients with measures of similar constructs, and conversely low and non-significant correlation with dissimilar constructs. There was also evidence of discriminant validity, with significant differences based on diagnostic status (participants with depression rated SIMS lower). Correlation coefficients on the SIMS between Times 1 and 2 were of moderate magnitude, with a small but statistically significant increase in mean ratings.

**Conclusions:** the data support the SIMS as a valid measure that can be administered to track changes in mood in clinical practice and research.

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Mood; measurement; single-item; depression; TBI

## Introduction

Following traumatic brain injury (TBI) there is an increased risk of emotional disorders, with elevated levels of depressed mood, irritability, apathy, and other neuropsychiatric symptoms (1). Clinicians and researchers require simple, valid, convenient, and repeatable measures to track day-to-day fluctuations in mood. This is in order to assess response to treatment and take a valid measure of mood, especially in cases where the patient/client has impaired communication.

A review of the literature found unclear evidence in relation to the validity of brief measures. Single-item mood scales (SIMS) are simple numeric, visual analogue, or pictorial instruments. SIMS can be used either as diagnostic tools where other, more complex tools are unsuitable (2), for example, in people with impaired communication, as well as ongoing measures for mood tracking. SIMS are a strong predictor of relapse in people with a history of major depressive disorder (3); however, results vary when this type of scale is applied to specific clinical populations, such as people with brain impairment.

There have been several studies of the use of a brief measure of mood in a stroke sample. Van Dijk and colleagues (4) undertook a systematic review of the studies previously conducted on instruments to identify depression in patients with aphasia after stroke and found all studies suffered from low methodological quality. Two of these studies administered a visual analogue scale of mood in a sample of stroke patients compared with common measures of depression such as the

Beck Depression Inventory (BDI), Hamilton Scale of Depression, Hospital Anxiety and Depression Scale, Geriatric Depression Scale, and the Structured Clinical Interview for the Diagnostic and Statistical Manual of the American Psychiatric Association (SCID) as validating instruments. The Van Dijk et al. review did not find the visual analogue scale to be a reliable diagnostic instrument for depression. Berg et al. (5) attempted to use a visual analogue mood scale as a dichotomous measure with “happy” and “sad” faces at the extreme ends of a line. They hypothesized that a response on the half of the line closer to the “sad” face would be equivalent to a diagnosis of depression, but they did not find significant agreement. When Berg et al. compared ratings on the visual analogue scale with the BDI they did find a relationship, but only at 18 months after a stroke, and they concluded that the visual scale was not a reliable indicator of the severity of depression symptoms. Tang et al. (5) found many participants did not understand the concept of a visual scale, which they attributed to advanced age and lack of education in their sample of stroke patients.

In contrast to the above studies, Turner-Stokes and colleagues (2) devised a six-point visual scale, the Depression Intensity Scale Circles (DISCs) as a diagnostic tool for depression in a mixed acquired brain injury (ABI) sample. They found acceptable agreement between the DISCs, formal diagnostic assessment (DSM-IV criteria), and the BDI. The DISCs are acceptable as a screening or diagnostic instrument; however, it may not be suitable for continuous mood tracking

because with only six points it might not identify subtle changes in mood. Another visual analogue scale used by Stern and colleagues (6) is the Visual Analogue Mood Scale (VAMS), a set of six 100-millimeter continuous scales, intended to provide a more sensitive indicator of change in mood. A drawback of the VAMS is that each of its six different emotions make a comparison against “neutral”. Happy and sad exist on separate scales and therefore it is not possible to track recovery from low mood on a single scale. Therefore, in developing the SIMS we sought to include these two opposing emotions on a single dimension in order to document not only an improvement in sad mood but also when a respondent started to feel happier and more positive. In contrast with the DISCs, we favored a format that could demonstrate changes in smaller increments by using continuous measurement along a visual analogue scale.

The aim of the study was to evaluate the psychometric properties of the SIMS in relation to criterion (also called concurrent) validity and construct validity (both discriminant validity and convergent/divergent validity), as well as temporal stability. We hypothesized that the SIMS in visual and verbal form would correlate with measures of related constructs (depressed mood and satisfaction with life) and not correlate with unrelated constructs. We also expected that scores on the SIMS would differ depending on the presence or absence of a current Major Depressive Episode (MDE). A recent study by Juengst and colleagues (7) showed that measuring mood at one time point may not capture day-to-day fluctuation in mood, thereby missing those in need of intervention. Therefore, the SIMS was administered with measures of related constructs on two occasions, between one and three weeks apart.

Following previous recommendations by our group (8), a “Levels of Evidence” approach was used to evaluate the standard of reporting, design, and statistical outcomes of the present study. The SIMS was evaluated using the COnsensus-based Standards for the selection of health Measurement INstruments Risk of Bias (COSMIN-RoB) scale (9) which includes criteria to assess design standards and statistical methods.

## Method

### Participants

Selection criteria comprised people who were living in the community, older than 18 years of age and with a history of TBI of any severity. Participants were identified by treatment providers who were either clinical psychologists, case managers, or occupational therapists working in private practice in metropolitan and rural areas of the state of New South Wales, Australia.

### Measures

#### *Single-item mood scale, visual (SIMS-visual)*

The SIMS-Visual is a single-item visual analogue scale, with a happy face symbol and a sad face symbol arranged vertically with a 100-mm line between them. The form was printed on

A4-sized paper (see Appendix A). Participants were instructed to draw a mark on a line, or point to a spot, in order to indicate their current mood. The vertical arrangement was chosen to minimize the impact of any unilateral spatial neglect and because thematically happy mood is associated with elevation, while sadness is associated with feeling “low” or “down.”

#### *Single-item mood scale, verbal (SIMS-verbal)*

The SIMS-Verbal is a single-item numeric rating scale, asking participants to rate their mood from zero to 10 where zero represented “your worst mood” and 10 “the best you have ever felt.” This was delivered in spoken format and recorded by the researcher. We accepted a respondent rating their mood between two numbers (e.g. “between 8 and 9” was recorded as 8.5).

### Validating instruments

#### *Structure clinical interview for DSM-5 disorders, clinical version (SCID-5) (10)*

The SCID-5 is considered the best practice assessment for clinical diagnosis and was used to determine the presence of a current MDE. The SCID-5 is a structured interview that allows the clinician or researcher to establish the presence or absence of DSM-5 diagnostic criteria. It is based on participants’ report and also on clinical observation. Participants were administered only “Module A: Mood Episodes” to establish the presence or absence of a current MDE. The SCID-5 manual provides a scoring template to determine whether criteria are met for a diagnosis of MDE.

#### *Depression anxiety and stress scales, 21-item version depression scale (DASS-D) (11)*

The DASS-D was chosen as a relevant depression scale with established psychometric properties for TBI. The DASS-D is one-third (7-items) of the DASS21 scale (which is a validated short form of the original DASS42). It lists various symptoms of depression (e.g. “I felt down-hearted and blue”) which are then endorsed on a four-point scale, from zero (the symptom did not apply) to 3 (the symptom was present “very much or most of the time”). The DASS21 responses are summed to provide a total score as per the scoring template produced by the authors. The range of scores on the scale is zero to 21 and higher scores are associated with greater distress; scores greater than 13 are classified as “extremely severe.”

Owensworth and colleagues (12) found the DASS-D depression scale component had acceptable internal consistency ( $r > 0.70$ ), test-retest reliability ( $r > 0.75$ ), and responsiveness ( $p < .01$ ) and was equivalent in psychometric properties to the full DASS42 depression subscale when used with an ABI sample. Concurrent validity with a similar measure (Hospital Anxiety and Depression Scale) was significant ( $r = 0.67, p < .05$ ). Randall, Thomas, Whiting, and McGrath (13) confirmed the original factor structure of the DASS21 when applied to TBI, further strengthening the validity of the DASS21 depression scale.

#### *Satisfaction with life scale (SWLS) (14)*

Life satisfaction is a construct which is a component of subjective well-being. It has a small correlation with current



mood and is more associated with general mood as a trait rather than occasion-specific mood (15). It consists of five items in which respondents indicate level of agreement with statements about life satisfaction (e.g. Item 1, “In most ways my life is close to my ideal” on a seven-point scale from strongly disagree to strongly agree). The SWLS has been widely used with TBI populations (16) and is part of the TBI Model Systems data set. The SWLS items are summed and yield a total score range from 5 (great dissatisfaction with life) to 35 (great satisfaction with life).

Hart and colleagues (17) found that the SWLS was associated with the diagnosis of major depression at one-year post-TBI and that there were significant differences between groups with no depression, minor depression, and major depression. The psychometric properties of the SWLS have not been comprehensively evaluated in a TBI sample. The initial study by Diener (14), conducted with a sample of university undergraduates, indicated that the SWLS is a stable measure with 2-month test–retest reliability of  $r = 0.82$  and is internally consistent (Cronbach’s alpha = 0.87). Reistetter and colleagues (18) found moderate concurrent validity with a correlation coefficient of  $r = 0.52$  with the Community Integration Measure in a combined sample of people with and without a history of ABI.

#### **World health organization disability assessment schedule, version 2.0 (WHODAS 2.0) (19)**

The WHODAS 2.0 was administered in order to provide descriptive information about the functional disability status of the sample and was also used to evaluate convergent/divergent validity of the SIMS. WHODAS 2.0 has 12- and 36-item formats which are either self-report or, proxy-report where capacity to respond is restricted. Each item of the WHODAS 2.0 asks the respondent to indicate the level of difficulty they experienced in each domain over the previous 30 days from zero (no difficulty) to four (extreme difficulty or cannot do). A scoring template is available which provides an overall percentage impairment. The WHODAS 2.0 calculates a percentage level of functional impairment with responses ranging from 0% to 97.92% (higher scores indicate greater impairment). In the current study, all participants completed the 12-item self-report version which explains 81% of the variance of the 36-item version ([https://www.who.int/classifications/icf/more\\_whodas/en/](https://www.who.int/classifications/icf/more_whodas/en/)). Andrews et al. (20) conducted a factor analysis and identified six domains within the WHODAS 2.0: cognition (items 3 and 6), mobility (items 1 and 7), self-care (items 8 and 9), social (items 10 and 11), society (items 4 and 5) and household (items 2 and 12).

Snell and colleagues (21) administered the WHODAS 2.0 to 79 patients with mild TBI and found high internal consistency (Cronbach’s alpha = 0.92). A subgroup of participants who met diagnostic criteria for major depression had approximately 40% higher scores on the WHODAS 2.0. A systematic review of psychometric studies of various WHODAS 2.0 versions found high test–retest reliability with intra-class correlation coefficients ranging from 0.80 to 0.92 across diverse samples (22). The WHODAS 2.0 had moderate to strong correlation with other measures of health status such as the

World Health Organization Quality of Life and Short-Form Health Questionnaire.

#### **Procedure**

Potential participants were initially contacted by staff of the recruiting sites who were not involved in the project. They gave potential participants the participant information sheet and consent forms for completion if they wished to participate. Where applicable, a legal guardian provided consent. Upon return of the completed consent form, the participant was contacted by a clinical psychologist and administered the full battery of measures in a face-to-face interview. Between one and three weeks later, the SIMS Verbal and SIMS Visual, the DASS21 and SWLS were re-administered in a face-to-face interview.

#### **Ethics approval**

Approval to conduct the study was granted by The University of Sydney Human Research Ethics Committee (Project No. 2017/482).

#### **Data analysis**

Scores for the SCID-5, DASS-D and SWLS questionnaires were calculated using standard templates. The SIMS Visual score was recorded by a measurement made in millimeters from the bottom of the vertical line to the participant’s mark. Raw scores and totals were entered into computer spreadsheets. Data analysis was conducted with SPSS v24 and data were screened for missing values and outliers. The data for continuous variables (SIMS Verbal and SIMS Visual) were evaluated for normality. SIMS Verbal (Time 1) and SIMS Visual (Times 1 and 2) demonstrated significant skewness. Transformations were attempted (square-root and log10) but they did not normalize the distributions. Consequently, non-parametric tests were conducted. In addition, the study included ordinal rating scales (DASS-D, WHODAS 2.0), further indicating the need for non-parametric statistics. The sample was split into sub-groups based on whether participants met or did not meet diagnostic criteria for MDE on the SCID-5. The subgroups were compared for injury and demographic variables using t-tests for continuous variables and chi-square for categorical variables.

#### **Measurement properties**

The study evaluated aspects of validity and temporal stability of the SIMS.

- a. Criterion (concurrent) validity refers to the extent to which a test measures a specific criterion; in this case, is the SIMS correlated with other measures of mood? It was analyzed with Spearman’s correlations for SIMS vs DASS-D and SWLS, and point-biserial correlations for SIMS vs SCID-5, a dichotomous outcome.
- b. Discriminant (construct) validity refers to the capacity of an instrument to discriminate between groups

with relevant characteristics; in this case, does the SIMS discriminate between MDE and non-MDE groups? We hypothesized that the MDE group will have lower scores on the SIMS than the non-MDE group. We also divided the sample into groups based on level of impairment as indicated by WHODAS 2.0 score using the median-split. We hypothesized that the low impairment group would have higher SIMS scores than the high impairment group. Mann-Whitney  $U$  tests were used to compare the independent samples.

- c. Convergent and divergent (construct) validity refers to the differential correlation of the instrument with similar versus dissimilar constructs. We hypothesized that the SIMS will correlate higher with WHODAS 2.0 item 5 “emotional”, than with WHODAS 2.0 item 1 “standing”, item 7 “mobility”, item 8 “washing” or item 9 “dressing”. We conducted Spearman’s rho correlations and made Bonferroni corrections to control for an inflated Type 1 error rate that can occur with multiple comparisons. The critical alpha level was thus set at  $p < .01$  (.05/5).
- d. Temporal stability refers to the stability of scores over time. As a state measure, SIMS is expected to change over time and we were interested in demonstrating this change rather than for SIMS to be shown to be “reliable”, i.e. fixed, from Time 1 to Time 2. This was evaluated with correlation coefficients (Spearman’s rho) and group comparisons (Time 1 vs Time 2) with the Wilcoxon Signed Rank Test.

### Quality rating

The methodological quality of this study was assessed using the COSMIN-RoB tool (9) which is a development of the original COSMIN design rating scale (23) that now includes assessment of statistical methods. Our group (8) has advocated using the method of Schellingerhout et al. (24) which combined COSMIN ratings with the “Terwee-m tool” for statistical methods. This method has been superseded by the recent update to the COSMIN-RoB which has been substantially altered in scope and purpose from the original COSMIN and has integrated some of the features of the Terwee-m.

The COSMIN-RoB distinguishes three domains of reliability, validity, and responsiveness in assessing the method quality of studies of patient-report outcome measures. The COSMIN-RoB tool consists of 10 “boxes”, each of which relates to a different measurement property across these three domains. The COSMIN manual (p.14) states that the COSMIN-RoB instrument should be used as a modular tool, in which quality standards and rating properties are only applied if that property has been measured in a particular study, because not all studies include assessment of all measurement properties. The COSMIN-RoB boxes applicable in the present study were Box 6 “reliability”, Box 7 “measurement error”, Box 8 “criterion validity”, and Box 9 “hypothesis testing for construct validity”. Box 9 included Box 9a “Comparison with other outcome measurement instruments (convergent validity)” and Box 9b “Comparison between subgroups (discriminant or known-

groups validity)”. Each box comprises between two and eight criteria for design standards and preferred statistical methods. Each criterion of the COSMIN-RoB tool is rated as “very good”, “adequate”, “doubtful”, “inadequate”, or “not applicable” against specified criteria. COSMIN uses the principle of “worst score counts” in order to provide a summary score for each box. Consequently, a scale that is rated “very good” for most criteria will be rated “inadequate” for a particular measurement property if it is found to be inadequate for even a single criterion.

## Results

### Participant characteristics

Descriptive statistics and demographic data are displayed in Table 1. Most participants were male, and the sample was highly variable in terms of age (range 18 to 86), injury severity (indicated by duration of post-traumatic amnesia (PTA) and length of hospitalization), and time since injury. Table 1 shows that the majority of participants had at least a high school level of education; approximately two-thirds were not in any paid employment. A high proportion was not currently in a relationship and almost two-thirds were living with their families. Nine participants (14.8%) had a history of injury or illness requiring hospitalization, 24.6% had a history of substance abuse and 19.7% had a history of mental illness prior to the TBI. In two cases an interpreter was required to assist with participation in the study and in each of those cases (one speaking Persian and the other Greek) it was possible to translate questionnaire items or use an existing translation of a questionnaire (e.g. DASS21). The sample was split into subgroups based on diagnostic status for MDE on the SCID. The subgroups were not found to be significantly different on any variable with the exception of PTA which was, on average, longer for the non-MDE subgroup.

Twenty participants (32.8%) met diagnostic criteria for a current MDE on the SCID-5. Table 1 displays the injury and demographics by each subgroup. There were four female participants in each subgroup (20% of MDE and 9.8% of non-MDE).

Table 2 shows the frequency of response categories for each WHODAS 2.0 item. The mean (SD) WHODAS score for the sample was 36.82% (22.74%) which equates to approximately the 10th percentile level of functional impairment (19).

#### a. Criterion (concurrent) validity

Correlation with MDE diagnostic status on the SCID-5 showed moderate point-biserial correlation coefficients with both SIMS-Verbal ( $r = -0.51$ ,  $p < .01$ ) and SIMS-Visual ( $r = -0.55$ ,  $p < .01$ ) at Time 1 (correlation with Time 2 was not conducted because the SCID-5 was administered only on one occasion at Time 1, and hence measures were not concurrent, which is an assumption of point-biserial correlations). At Time 1, SIMS-Verbal and SIMS-Visual were highly inter-correlated (Table 3), and there were moderate correlations between both versions of the SIMS with the DASS-D and SWLS. These findings were

**Table 1.** Descriptive statistics.

	No MDE (N = 41)	MDE (N = 20)	Overall sample (N = 61)	Statistical analysis	
	Mean (SD)	Mean (SD)	Mean (SD)	t-test	Significance
Age	42.20 (15.20)	35.6 (16.7)	40.03 (15.89)	t (59) = 1.54	.129
Years since TBI	5.71 (5.46)	6.76 (8.68)	6.05 (6.63)	t (59) = -.58	.565
PTA duration (days)~	85.31 (70.21)	45.58 (46.71)	71.82 (65.55)	t (51) = 2.16	.018*
Weeks of hospitalization	26.49 (19.56)	16.56 (14.23)	23.24 (18.47)	t (56) = 1.97	.054
	N (%)	N (%)	N (%)	Chi-square	Significance
Sex					
Female	4 (9.8%)	4 (20%)	8 (13.1%)	$\chi^2 = 1.24$	.266
Male	37 (90.2%)	16 (80%)	53 (86.9%)		
Education <sup>^</sup>					
Primary school	2 (4.9%)	1 (5%)	3 (4.9%)	$\chi^2 = 5.85$	.119
High school	19 (46.3%)	15 (75%)	34 (55.7%)		
Trade certificate	8 (19.5%)	3 (15%)	11 (18.0%)		
University	12 (29.3%)	1 (5%)	13 (21.3%)		
Employment					
Not employed	26 (63.4%)	11 (55%)	37 (60.7%)	$\chi^2 = 2.84$	.417
Student	1 (2.4%)	2 (10%)	3 (4.9%)		
Volunteering	2 (4.8%)	0 (0%)	2 (3.3%)		
Employed	12 (29.3%)	7 (35%)	19 (31.1%)	$\chi^2 = 2.39$	.495
Relationship status	18 (43.9%)	11 (55%)	29 (47.5%)		
Single	12 (29.3%)	7 (35%)	19 (31.1%)		
Married/defacto	10 (24.4%)	2 (10%)	12 (19.7%)		
Separated/divorced	1 (2.4%)	0 (0%)	1 (1.6%)	$\chi^2 = 6.52$	.089
Widowed					
Living situation					
Alone	10 (24.4%)	2 (10%)	12 (19.7%)		
With family	22 (53.7%)	17 (85%)	39 (63.9%)		
Share house	3 (7.3%)	1 (5%)	4 (6.6%)		
Supported living	6 (14.6%)	0 (0%)	6 (9.8%)		

~ In cases where PTA testing was discontinued, due to ongoing and global cognitive impairment at 6 months post-trauma, this was recorded as equivalent to 182 days.

<sup>^</sup> Education level. Primary school = completed up to 9 years of school. High school = at least 10 years of school (matriculation level). Trade = trade qualification. University = completed undergraduate or postgraduate degree.

\*  $p < 0.05$ .

**Table 2.** Frequency of response on WHODAS 2.0 items.

Domain (20)	Item No.	Category	(0) No difficulty n (%)	(1) Mild difficulty n (%)	(2) Moderate difficulty n (%)	(3) Severe difficulty n (%)	(4) Extreme diff./ can't do n (%)	Mean (SD)	Median (IQR)
Mobility	1	Standing	31 (50.8%)	4 (6.6%)	9 (14.8%)	3 (4.9%)	14 (23.0%)	1.43 (1.67)	0 (3)
	7	Mobility	29 (47.5%)	8 (13.1%)	7 (11.5%)	3 (4.9%)	14 (23.0%)	1.43 (1.65)	1 (3)
Household	2	Household	22 (36.1%)	11 (18.0%)	6 (9.8%)	9 (14.8%)	13 (21.3%)	1.67 (1.60)	1 (3)
	12	Work	11 (18.0%)	5 (8.2%)	8 (13.1%)	7 (11.5%)	30 (49.2%)	2.66 (1.58)	3 (3)
Cognitive	3	Learning	21 (34.4%)	13 (21.3%)	14 (23.0%)	8 (13.1%)	5 (8.2%)	1.39 (1.31)	1 (2)
	6	Concentration	16 (26.2%)	13 (21.3%)	20 (32.8%)	9 (14.8%)	3 (4.9%)	1.51 (1.18)	2 (2)
Society	4	Participating	19 (31.1%)	14 (23.0%)	12 (19.7%)	10 (16.4%)	6 (9.8%)	1.51 (1.35)	1 (3)
	5	Emotional	13 (21.3%)	9 (14.8%)	11 (18.0%)	25 (41.0%)	3 (4.9%)	1.93 (1.3)	2 (2)
Self-care	8	Washing	42 (68.9%)	6 (9.8%)	3 (4.9%)	1 (1.6%)	9 (14.8%)	0.84 (1.46)	0 (1)
	9	Dressing	39 (63.9%)	7 (11.5%)	4 (6.6%)	4 (6.6%)	7 (11.5%)	0.90 (1.42)	0 (2)
Social	10	Dealing with people	24 (39.3%)	14 (23.0%)	12 (19.7%)	7 (11.5%)	4 (6.6%)	1.23 (1.27)	1 (2)
	11	Friendships	26 (42.6%)	10 (16.4%)	13 (21.3%)	6 (9.8%)	6 (9.8%)	1.28 (1.37)	1 (2)
WHODAS Overall Summary Score								36.82% (22.74%)	31.25% (31.25%)

**Table 3.** Spearman's rho correlation coefficients, separate analyses at each time point.

Correlation	Time 1 (n = 61)	Time 2 (n = 58)
SIMS Verbal vs SIMS Visual	.88**	.92**
SIMS Verbal vs DASS21-D	-.52**	-.62**
SIMS Visual vs DASS21-D	-.52**	-.61**
SIMS Verbal vs SWLS	.50**	.58**
SIMS Visual vs SWLS	.52**	.66**

\*\* Significant at  $<0.01$ .

replicated at Time 2 but with higher correlation coefficients.

#### b. Discriminant (construct) validity

**Table 4** displays descriptive data and comparisons to evaluate discriminant (construct) validity of the SIMS for participants grouped by diagnostic status on the SCID-5. There were significant differences between participants based on diagnostic status and these were in expected directions with moderate effect sizes. SIMS-Verbal, SIMS-Visual, and SWLS were rated lower for participants with MDE (indicating lower mood for participants currently experiencing a depressive episode) and DASS-D was rated higher

**Table 4.** Repeated measures by MDE diagnostic status on the SCID – descriptive statistics and Mann–Whitney *U* test.

Measure	No MDE (n = 41)		MDE diagnosis (n = 20)		Mann–Whitney <i>U</i> test
	Mean (SD)	Median (IQR)	Mean (SD)	Median (IQR)	Z statistic (p)/Effect size
SIMS Verbal					
Time 1	6.96 (1.67)	7.00 (2.10)	4.53 (2.47)	4.00 (3.00)	–3.84 (.00)/.49
Time 2	7.62 (1.75)	8.00 (2.60)	5.13 (2.22)	5.00 (3.00)	–3.89 (.00)/.50
SIMS Visual					
Time 1	6.86 (1.96)	7.15 (3.18)	3.90 (2.51)	4.30 (2.90)	–4.26 (.00)/.55
Time 2	7.58 (2.01)	8.15 (1.55)	4.21 (2.79)	4.30 (4.60)	–4.25 (.00)/.54
DASS-D					
Time 1	8.93 (9.60)	8.00 (16.00)	27.10 (10.83)	26.00 (20)	–4.97 (.00)/.64
Time 2	7.52 (8.81)	4.00 (13.00)	24.32 (12.35)	26.00 (20)	–4.49 (.00)/.57
SWLS					
Time 1	20.80 (7.42)	21.00 (14.00)	11.50 (4.65)	13.00 (9.00)	–4.25 (.00)/.54
Time 2	22.15 (9.23)	23.00 (16.00)	12.42 (5.53)	13.00 (10.00)	–3.78 (.00)/.48

(indicating greater depression symptoms). This was shown at each time point.

Table 5 displays the comparison between “low” and “high” impairment groups based on WHODAS 2.0 score. We used the WHODAS rather than another clinical indicator (e.g. PTA duration) because it was available for the entire sample and it was a better reflection of current functional capacity. Using the median of 31.25% (equivalent to the 5<sup>th</sup> percentile of functional impairment by comparison with the non-clinical normative sample) participants were divided into “low” and “high” impairment groups. This showed a small but statistically significant effect at Time 1, such that high impairment was associated with lower SIMS and SWLS scores. This effect was smaller and not statistically significant at Time 2.

#### c. Convergent and divergent (construct) validity

Table 6 reports correlations between the SIMS and items on the WHODAS 2.0. As hypothesized, there was a significant correlation between the SIMS and the “emotional” functioning item but not with four other ‘non-emotional’ items of the WHODAS 2.0, in particular, those related to mobility (items 1 and 7) and self-care (items 8 and 9).

#### d. Temporal stability

Table 7 displays descriptive data, correlation coefficients, and comparisons by time for the repeated measures (SIMS-Visual, SIMS-Verbal, DASS-D, and SWLS).

Standard error of measurement (SEM) is displayed for each measure. The results found that all measures were significantly correlated from Time 1 to Time 2 with moderate-to-high coefficients. There were small but statistically significant differences (Wilcoxon Signed Rank Test)

**Table 6.** Spearman’s rho correlations between WHODAS 2.0 items and SIMS at time 1 (*N* = 61).

Domain (as per Andrews 2009)	Item No.	Category	SIMS Verbal <i>r</i> (p)	SIMS Visual <i>r</i> (p)
Mobility	1	Standing	–.169 (.193)	–.126 (.332)
	7	Mobility	–.130 (.319)	–.161 (.216)
Household	2	Household	–.181 (.162)	–.157 (.226)
	12	Work	–.021 (.873)	–.023 (.862)
Cognitive	3	Learning	–.112 (.389)	–.236 (.067)
	6	Concentration	–.160 (.219)	–.187 (.149)
Society	4	Participating	–.163 (.211)	–.152 (.243)
	5	Emotional	–.494 (.000) *	–.460 (.000) *
Self-care	8	Washing	–.042 (.747)	–.120 (.356)
	9	Dressing	–.140 (.281)	–.179 (.168)
Social	10	Dealing with people	–.088 (.498)	–.109 (.401)
	11	Friendships	–.305 (.017)	–.358 (.005)

\*Significant result with Bonferroni correction  $\alpha = 0.05/5 = 0.01$ .

**Table 5.** Repeated measures by impairment level measured by the WHODAS – descriptive statistics and Mann–Whitney *U* test.

Measure	Low WHODAS (n = 32)		High WHODAS (n = 29)		Mann–Whitney <i>U</i> test
	Mean (SD)	Median (IQR)	Mean (SD)	Median (IQR)	Z statistic (p)/Effect size
SIMS Verbal					
Time 1	6.86 (1.76)	7.00 (2.00)	5.40 (2.52)	5.00 (3.30)	–2.35 (.02)/.30
Time 2	7.23 (1.85)	7.00 (2.8)	6.30 (2.56)	6.25 (2.56)	–1.48 (.14)/.19
SIMS Visual					
Time 1	6.64 (2.14)	7.05 (3.58)	5.06 (2.74)	4.95 (5.10)	–2.14 (.03)/.27
Time 2	7.01 (2.25)	7.55 (2.83)	5.81 (3.23)	6.95 (5.70)	–1.19 (.23)/.15
DASS-D					
Time 1	11.31 (9.66)	11.00 (18.00)	18.83 (15.36)	17.00 (31.00)	–1.93 (.06)/.25
Time 2	11.19 (9.28)	11.00 (14.00)	15.31 (15.97)	8.00 (33.00)	–.43 (.67)/.06
SWLS					
Time 1	19.50 (7.58)	18.00 (14.00)	15.83 (8.00)	14.00 (13.00)	–1.93 (.05)/.25
Time 2	19.81 (7.68)	19.50 (11.00)	17.92 (11.18)	14.50 (20.00)	–1.16 (.25)/.15



**Table 7.** Repeated measures by time – mean (SD), Spearman's rho correlation coefficients, and Wilcoxon signed-rank test comparisons.

Measure	Time 1 N = 61		Time 2 N = 58		Spearman's rho	Wilcoxon Signed Rank Test
	Mean (SD)	Median (IQR)	Mean (SD)	Median (IQR)	$r_s$ (p) SEM	Z (p) Effect size
SIMS Verbal	6.16 (2.26)	6.50 (3.00)	6.83 (2.23)	7.00 (3.00)	.61 (.00) 1.41	–3.21 (.00).42
SIMS Visual (cm)	5.89 (2.55)	6.30 (3.45)	6.53 (2.76)	7.20 (3.75)	.70 (.00) 1.40	–3.38 (.00).44
DASS21 Depression	14.89 (13.14)	14.00 (19.00)	12.91 (12.85)	10.00 (18.00)	.77 (.00) 6.30	–2.10 (.04).28
SWLS	17.75 (7.93)	17.00 (13.00)	18.86 (8.70)	19.00 (15.00)	.79 (.00) 3.63	–1.08 (.28).14

between Time 1 and Time 2 on the SIMS-Verbal, SIMS-Visual which were rated higher (indicating more elevated mood), and the DASS-D which was rated lower (indicating less depressive symptomatology). There was no significant difference related to time on the SWLS.

### Quality rating

The COSMIN-RoB checklist was applied as it related to the SIMS study. A full explanation of the ratings is contained in the evidence table (Appendix B).

- Reliability. Box 6 was applied because we had evaluated the Temporal Stability of the SIMS. This was rated as “inadequate” because scores on SIMS were not stable (i.e. they were significantly different) between Time 1 and Time 2. We note that mood is a state measure which is not expected to be as consistent over time as a trait measure.
- Measurement error was evaluated by a calculation of SEM. Box 7 was applied and again this was rated “inadequate” because scores on SIMS were not stable (i.e. they were significantly different) between Time 1 and Time 2.
- Criterion (concurrent) validity. Box 8 was rated “very good” because of the use of recommended statistical analyses (correlations).
- Discriminant (construct) validity. Box 9b was rated “very good” on the basis that demographic and injury characteristics for the two sub-groups were provided and analyses were conducted to determine if differences were significant. The subgroups were not significantly different on any characteristic except for one measure of injury severity (PTA duration).
- Convergent and divergent (construct) validity. This was rated “very good” on Box 9a due to the inclusion of an appropriate comparator measure (the WHODAS 2.0) and appropriate statistical analyses demonstrating the direction of correlations was as hypothesized.

### Discussion

There was a high level of agreement between verbal and visual forms of the SIMS (Time 1,  $r = 0.88$  and Time 2,  $r = 0.92$ ). Criterion (concurrent) validity was demonstrated by moderate correlation coefficients between the SIMS and diagnostic status, and between the SIMS and other mood-related

measures (DASS-D and SWLS). This suggests that the SIMS measured constructs that were related, but not exactly the same. This is to be expected because a diagnosis of depression is not made purely on reports of mood. There are other symptoms of depression in addition to low mood, such as difficulty concentrating, which could be attributable to other factors (such as cognitive sequelae of TBI). When the sample was divided into groups depending on the presence or absence of a major depressive episode, there were significant differences in SIMS ratings, providing support for the discriminant validity of the SIMS.

SIMS ratings changed from Time 1 to Time 2 (tending to increase) and this change was statistically significant with moderate effect sizes. There was also a small but significant effect for DASS-D scores, but no significant change in SWLS. This was an important finding and was consistent with the SIMS being a measure of current state and the DASS-D addressing the recent past (over the previous week). Conversely, the SWLS asks the participant to reflect on his/her lifetime and would be expected to be more stable. Following recent findings of Juengst and colleagues (7) – that measuring mood at one time might not reflect an individual's overall mood state – it is useful to have a measure which is sufficiently flexible to capture respondents' mood from frequent, repeated ratings. From a clinical perspective, this is very helpful for applications such as Behavioral Activation Therapy (25) in which the clinician tries to help their patients find meaningful, rewarding daily activities by frequent measurement of mood.

A welcome finding was the relative equivalence of verbal and visual forms of the SIMS, indicating that when selecting the form to be used this should be based on the needs of the respondent rather than concern about which version is more valid. The participant group reflected a diverse range of injury severity and functional capability which were found to affect SIMS scores, albeit to a slight degree with small effect sizes that were not shown consistently across time. SIMS Visual might have useful cross-cultural applications and may be advantageous for people with communication disorders or lower levels of functioning. The comparison with the items of the WHODAS 2.0 demonstrated that the SIMS was unrelated to deficits in day-to-day functioning in all domains measured, except for the item that could reasonably be expected to be related to mood (viz., emotional functioning). Given that the WHODAS 2.0 is a self-report instrument, it does not provide an objective, performance-based assessment

of the participants' levels of impairment across cognitive domains. Accordingly, it is possible that cognitive function as measured by objective, performance-based cognitive tests could yield a different result. A future study could evaluate the psychometric properties of the SIMS in relation to objective performance-based cognitive tests.

We applied quality rating criteria to our evaluation of the SIMS using the COSMIN-RoB scale. Ratings were "very good" as it applied to validity. The current study found that ratings on repeated measures changed over time and, as such, did not demonstrate strong temporal stability of the SIMS. This is not necessarily problematic when evaluating a mood state measure, but a shorter test–retest interval might have demonstrated greater reliability (e.g. (26,27)). The reasons for the change in mood from Time 1 to Time 2 are unclear but were not due to intended manipulation such as a treatment effect. A future study could investigate the responsiveness of the SIMS in a treatment evaluation study in which it is compared to other outcome measures.

The SIMS shows promise for further development in various ways. Beyond the emotions of 'happy' and 'sad' the SIMS could be expanded to include other emotions along dimensions such as self-regulation (e.g., 'aggressive/passive'; 'agitated/lethargic'). The SIMS format lends itself to electronic data collection and a future study could administer the SIMS as a smartphone application.

In conclusion, we sought to evaluate SIMS amongst a varied sample of people with TBI living in metropolitan and regional New South Wales, Australia. The SIMS were found to agree significantly with measures of similar constructs (depression, life satisfaction) and performed in the expected directions when participants were classified by the presence of a Major Depressive Episode or by their level of functional impairment. The study was evaluated for method quality and it was found to demonstrate very good methodology for aspects of validity. Upon this basis, we recommend the use of SIMS as simple and convenient measures for the tracking of mood in research and clinical practice.

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## Disclosure of Interest

The authors are not aware of any interests that might affect the current study.

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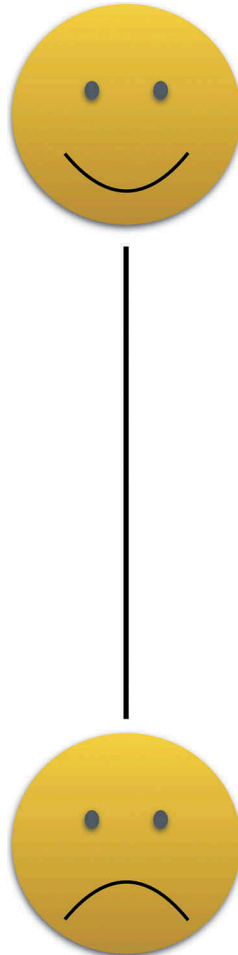
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## Appendix A – SIMS Visual form

Visual mood scale (sad to happy)

Instructions: "Please indicate how you feel right now along this line from happy (point to top) to sad (point to bottom). Indicate by pointing or drawing a mark."





## Appendix B: COSMIN Risk of Bias checklist

### Box 6. Reliability.

Item	Standard <i>Design requirements</i>	Rating <i>COSMIN criteria</i>	Rationale
1	Were patients stable in the interim period of the construct to be measured?	Inadequate	Participants' scores on SIMS were not stable from Time 1 to Time 2
2	Was the time interval appropriate?	Very good	Time interval was between 1 and 3 weeks for all participants and the COSMIN manual specifies that 2 weeks is ideal. Furthermore, 1–3 weeks was considered an appropriate interval to allow for typical fluctuations in mood.
3	Were the test conditions similar for the measurements?	Very good	Test conditions were the same or very similar from Time 1 to Time 2
	<i>Statistical methods</i>		
4	For continuous scores: was an intraclass correlation coefficient calculated?	Doubtful	Spearman correlation coefficient calculated with evidence that systematic change has occurred
5, 6, 7	For dichotomous, ordinal, nominal scores	Not applicable	
8	Were there any other important flaws in the design or statistical methods of the study?	Very good	Nil identified
	Overall score	Inadequate	

### Box 7. Measurement Error.

Item	Standard <i>Design requirements</i>	Rating <i>COSMIN criteria</i>	Rationale
1	Were patients stable in the interim period of the construct to be measured?	Inadequate	Participants' scores on SIMS were not stable from Time 1 to Time 2
2	Was the time interval appropriate?	Very good	Time interval was between 1 and 3 weeks for all participants and the COSMIN manual specifies that 2 weeks is ideal. Furthermore, 1–3 weeks was considered an appropriate interval to allow for typical fluctuations in mood.
3	Were the test conditions similar for the measurements?	Very good	Test conditions were the same or very similar from Time 1 to Time 2
	<i>Statistical methods</i>		
4	For continuous scores: Was the Standard Error of Measurement (SEM), Smallest Detectable Change (SDC) or Limits of Agreement (LoA) calculated?	Very good	SEM calculated
5	For dichotomous, ordinal, nominal scores	Not applicable	
	Overall score	Inadequate	

### Box 8. Criterion validity.

Item	Standard <i>Statistical methods</i>	Rating <i>COSMIN criteria</i>	Rationale
1	For continuous scores: were correlations, or the area under the receiver operating curve calculated?	Very good <i>Correlations were calculated</i>	Spearman's correlations were conducted with measures of similar constructs
2	For dichotomous scores	Not applicable	
3	Were there any other important flaws in the design or statistical methods of the study?	Not applicable	In previous versions of the COSMIN it was a requirement to have a comparison with a "Gold Standard" measure, however the 2018 version of the COSMIN-RoB has removed this requirement in acknowledgment that Gold Standards rarely exist for Patient-Report Outcome Measures.
	Overall score	Very good	

**Box 9.** Hypotheses testing for construct validity.

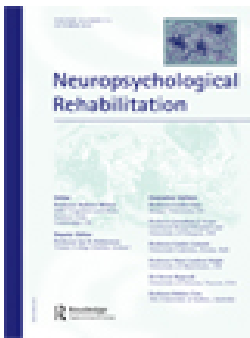
9a. Comparison with other outcome measurement instruments (convergent validity)			
Item	Standard <i>Design requirements</i>	Rating <i>COSMIN criteria</i>	Rationale
1	Is it clear what the comparator instruments measures?	Very good <i>Constructs measured by the comparator instruments are clear.</i>	The measure chosen as it relates to hypothesis testing was the WHODAS 2.0. This is described in the Methods section.
2	Were the measurement properties of the comparator instrument sufficient?  <i>Statistical methods</i>	Very good <i>Sufficient measurement properties of the comparator instruments in a population similar to the study population.</i>	The description of the WHODAS 2.0 includes reference to a study of a similar population (mild TBI) with the same subgroups based on diagnostic status (meets criteria for MDE or doesn't meet criteria). This study reports high internal consistency and test-retest reliability.
3	Was the statistical method appropriate for the hypotheses to be tested?	Very good <i>Statistical method was appropriate</i>	Use of Spearman's correlations supported by presentation of measures of mean, median and variance. In addition, we have relied not just on <i>p</i> values but evaluated the magnitude and direction of correlations.
4	Were there any other important flaws in the design or statistical methods of the study?  Overall score	Very good <i>No other important methodological flaws</i>  Very good	
9b. Comparison between subgroups (discriminant or known-groups validity)			
Item	Standard <i>Design requirements</i>	Rating <i>COSMIN criteria</i>	Rationale
5	Was an adequate description provided of important characteristics of the subgroups?  <i>Statistical methods</i>	Very good <i>Adequate description of the important characteristics of the subgroups</i>	The sample is described overall and then they were administered the SCID which determined their demographic or injury characteristics as per <a href="#">Tables 1</a> and <a href="#">2</a> . The injury and demographic characteristics were described and statistical comparisons of the subgroups were conducted.
6	Was the statistical method appropriate for the hypotheses to be tested?	Very good <i>Statistical method was appropriate</i>	Mann-Whitney <i>U</i> was applied to the comparison which was appropriate considering the comparator variable (diagnostic status) was dichotomous (SCID). In addition, point-biserial correlations are presented for the data at Time 1, again this was considered appropriate for a comparison between a dichotomous variable and a continuous variable.
7	Were there any other important flaws in the design or statistical methods of the study?  Overall score	Very good <i>No other important</i>  Very good	

## CHAPTER 5

***Behavioural activation therapy to improve participation in adults with depression following brain injury: a single-case experimental design study***

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# Behavioural activation therapy to improve participation in adults with depression following brain injury: A single-case experimental design study

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# Behavioural activation therapy to improve participation in adults with depression following brain injury: A single-case experimental design study

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## ABSTRACT

Following brain injury, the risk of depression increases. There are few studies of non-pharmacological interventions for this problem. Behavioural Activation (BA) could help because it has been demonstrated to be as effective as cognitive-behaviour therapy but is less cognitively demanding and more suitable for people with brain impairment. The current study evaluated BA using a multiple-baseline design across behaviours with replication. Three male participants with clinically significant depressive symptoms (two with traumatic brain injury aged 26 and 46, one who experienced strokes in infancy, aged 26) engaged in a 10-14-week trial of BA focusing on three activity domains: physical, social and functional activities. Participants completed an online form three times a day which recorded activity participation and responses to a single-item mood scale. There was little evidence in support of BA for increasing participation. There was also a lack of change in average mood, but some positive effects were found on measures of depression symptoms and quality of life in these participants. Various factors affected participation which might have been mitigated by extended treatment contact, greater use of prompts or electronic aids or the addition of other therapy modes.

## ARTICLE HISTORY



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## KEYWORDS

Acquired brain injury; Behavioural activation; Major depressive disorder; Single-item mood scale; Single case experimental design

## Introduction

There is increased risk of depression following acquired brain injury. Depression occurred in more than half of all patients in the first year after traumatic brain injury (TBI; Bombardier et al., 2010) and was found to persist several years later (Dikmen, Bombardier, Machamer, Fann, & Temkin, 2004; Kreutzer, Seel, & Gourley, 2001). Depression is a problem not only because of the distress associated with it, but also because it is negatively associated with everyday

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functioning (Chaytor, Temkin, Machamer, & Dikmen, 2007) and participation outcomes such as return to work (Garrelfs, Donker-Cools, Wind, & Frings-Dresen, 2015). Juengst, Kumar, and Wagner (2017) found that depression untreated at six-months post-injury predicted further depression at 12 months through a perpetuating cycle of mood and behavioural dysfunction.

There is limited agreement about the best approaches for managing depression after brain injury, either pharmacologically or non-pharmacologically (Juengst et al., 2017). In our Cochrane systematic review, we found no evidence in support of any non-pharmacological treatment (Gertler, Tate, & Cameron, 2015). When the data for the eligible studies were combined ( $n = 146$ ), there was no reliable effect in support of psychological therapy (such as cognitive-behaviour therapy, CBT, or mindfulness training). Since the publication of Gertler et al. (2015), there has been a further randomized controlled trial demonstrating the benefit of CBT in reducing symptoms of depression after brain injury, the critical ingredient appears to be the provision of booster sessions some months after intensive treatment ended (Ponsford et al., 2016).

Behavioural Activation (BA) therapy was developed as a brief and uncomplicated intervention and has proven efficacy in the treatment of depression across different age and clinical groups including dementia patients (Cuijpers, van Straten, & Warmerdam, 2007). BA evolved from the work of Jacobson et al. (1996) who found that the behavioural activation components of CBT performed as well as full CBT. Lejuez and colleagues then developed and refined a treatment manual for BA (Lejuez, Hopko, & Hopko, 2001; Lejuez, Hopko, Acierno, Daughters, & Pagoto, 2011). Compared to other modes of treatment, BA may be more appropriate for people with cognitive impairment after brain injury because of the focus on behavioural rather than cognitive strategies. It is less dependent on language and has proven successful for treating depression in people with aphasia following stroke (Thomas, Walker, MacNiven, Haworth, & Lincoln, 2012). In contrast, treatments such as CBT or Acceptance and Commitment Therapy (ACT) may require flexibility in thinking often beyond the capacity of some people with cognitive impairment after brain injury. Whiting, Deane, McLeod, Ciarrochi, and Simpson (2019) evaluated ACT and found reduction in depression symptoms but no significant improvement in cognitive flexibility which is a key target of ACT. A suggested explanation for the improvement in mood was behavioural activation from engagement in treatment.

The aim of the current study was to investigate whether BA improves activity participation and mood for people with depression following brain injury. It was hypothesized that increased participation in activities would lead to an improvement in daily mood. Three broad categories of activity were investigated (physical, social and functional) with the aim of determining whether different types of activity focus led to increased participation and/or mood ratings.

## Method

### *Research design*

The current study was designed to meet standards for the methodology of SCEDs (Kratochwill et al., 2013; Tate et al., 2013a). The report was prepared according to SCRIBE criteria (Tate et al., 2016). The trial was registered with the Australian New Zealand Clinical Trials Registry (trial number ACTRN12613001166763) prior to the recruitment of participants.

The design used a multiple-baseline design across three behaviours with replication across two participants. One author (PG) administered the outcome measures and the BA intervention and another author (RLT) coordinated the randomization of the target behaviour (TB) order using a computer-generated list. Secondary and generalization measures were administered at the beginning of the data collection period and at selected points during the intervention, corresponding to the end of the treatment phase in each tier.

### *Participant selection*

The current study was approved by the Human Research Ethics Committee of The University of Sydney (protocol no. 14939). Participants were included if they were community-dwelling adults who had cognitive impairments due to a brain injury and had been referred to a clinical psychology practice for the purpose of treating symptoms of depression. Participants were not excluded on the basis of additional diagnoses, drug/alcohol dependence or physical incapacity. The three participants were considered to reflect the complexity of cases that are referred to a community-based private practice and each had similar histories to several other cases that have presented to the practice in the past 20 years.

### *Target behaviours (TB)*

The TBs were selected by each participant in consultation with the therapist (PG). These related to each participant's personal and rehabilitation goals, as is compatible with BA philosophy. The participants identified TBs within three domains, which formed the tiers of the multiple-baseline design: physical activities, social activities and functional independence tasks as defined by codes of the International Classification of Functioning, Disability and Health (ICF; World Health Organisation, 2001) within the Activities and Participation component (specifically, categories within the domains of mobility; domestic life; interpersonal interactions and relationships; communication; community, social and civic life; and education, work and employment).

### *Target behaviour 1: Physical activities*

Each participant identified increasing their physical fitness as a personal priority, and there is evidence of an association between level of physical activity and depression after brain injury (Driver & Ede, 2009; Hoffman et al., 2010). Physical activity was defined as any participation activity which involved physical exertion (irrespective of the level of vigour) such as gym sessions, going for a walk (ICF codes d9201 “sports” and d450 “walking and moving” respectively), or activities that involved incidental physical activity such as gardening (ICF code d6505 “taking care of plants”). Activities combining multiple physical activities, such as a gym routine, counted as a single activity.

### *Target behaviour 2: Social activities*

Each participant wanted to increase their engagement with other people as they identified this as important and enjoyable. The TB was the recorded frequency of contact with other people face-to-face, or communicating with friends and family over the phone, via Skype, email and Facebook irrespective of duration (ICF codes d750 “informal social relationships”, d910 “community life” and d9205 “socializing”). This included spending time with people with whom the participant had become familiar with over time, e.g., the staff in a local café. It did not include appointments with professionals or interactions with strangers, e.g., people working in a shop with whom there was only brief contact.

### *Target behaviour 3: Functional independence or vocational task completion*

Each participant identified completion of functional independence tasks as consistent with their personal values. The TB was the number of distinct functional independence tasks (not including personal care, cf. ICF domain d5 “self-care”) including food preparation, house cleaning and taking rubbish from the kitchen to bins outside (ICF domain d6 “Domestic life” not including d6505 “taking care of plants”). For one participant (Mr Z) this included improving his vocational skills and job seeking (ICF categories of d825 “vocational training”, d8450 “seeking employment” and d855 “non-remunerative employment”).

## *Measures*

Participants completed a Daily Activity Log (DAL) using a computer or smart-phone three times a day (morning, afternoon and night). Participants recorded their performance of activities related to the three TBs. Data from the DALs were assessed for frequency of TBs by two raters: the therapist (PG) who used this data to inform treatment during the study, and an independent rater (ALB) to establish inter-rater reliability. Inter-rater reliability was moderate ( $\kappa = 0.65$ ,  $p < 0.001$ ). Participants rated their mood on a 10-point Likert scale (from 1 to 10); a low score was associated with depressed mood and high scores associated with positive mood. We have evaluated the psychometric



qualities of single-item mood scales in a separate study and found them to have acceptable criterion and construct validity in a brain injury sample (Gertler & Tate, in submission). Mr X rated his level of pain on a similar Likert scale.

### *Secondary and generalization measures*

The seven-item depression subscale of the Depression, Anxiety and Stress Scales (DASS21; Lovibond & Lovibond, 1995) was chosen as a validated self-report measure of depression which has acceptable psychometric properties: internal consistency (Cronbach's  $\alpha = 0.88$ ), test-re-test reliability ( $r = 0.78$ ,  $p = 0.019$ ; Ownsworth, Little, Turner, Hawkes, & Shum, 2008) and valid factor structure for brain injury (Randall, Thomas, Whiting, & McGrath, 2017).

Three measures were administered as *a priori* generalization measures. Self-esteem, quality of life and satisfaction with life were all likely to have been affected as a secondary consequence of ABI and depression. Self-esteem was assessed using the 10-item Rosenberg Self-Esteem Scale (Rosenberg, 1965). This scale has high internal consistency (Cronbach's  $\alpha = 0.91$ ; Sinclair et al., 2010) and widespread use including in ABI (Anson & Ponsford, 2006; Kelly, Ponsford, & Couchman, 2013; Simpson, Tate, Whiting, & Cotter, 2011).

The 37-item Quality of Life After Brain Injury (QOLIBRI; von Steinbüchel, Petersen, & Bullinger, 2005) measures health-related quality of life following brain injury. The QOLIBRI has demonstrated construct validity and test-retest reliability in this population (von Steinbuechel et al., 2012).

The 5-item Satisfaction with Life scale (SWLS; Diener, Emmons, Larsen, & Griffin, 1985) measures "global life satisfaction". Corrigan, Kolakowsky-Hayner, Wright, Bellon, and Carufel (2013) have confirmed its construct validity in a brain-impaired sample.

### *Procedure and treatment methods*

Behavioural Activation Therapy followed the revised treatment manual by Lejuez et al. (2011) which provides structure and content for 10 sessions (30–90 min each; see table in Online Appendix A). Treatment can be extended by repeating session content. For Mr X and Mr Y, the treatment was extended to 14 weeks in order to allow sufficient time for them to develop strategies specific to the TBs. Sessions were conducted in their homes in order to increase compliance with treatment. Treatment sessions were videorecorded and took place in their lounge rooms. Mr X sat in a wheelchair and Mr Y sat on a couch with the therapist facing them with a dSLR camera on tripod recording so that the participant's face was not seen. Mr Z's treatment was funded by a public health access programme (Medicare) which funded only 10 sessions in the therapist's office. He sat across a desk from the therapist with a computer set to record audio. As part of the intervention, participants were required to schedule out-of-session activities in their homes and communities.

Once the participants were familiar with the procedures, baseline monitoring commenced. Baseline monitoring was extended into sessions 1 and 2 of the BA programme because during this time the treatment protocol specified that participants were to maintain their current activities. Accordingly, for the purpose of recording the TB, session 3 became the first datapoint of the intervention phase.

### *Treatment adherence*

A registered psychologist (ALB) conducted an independent review of video and audio recordings of the treatment sessions. A session was reviewed for each week of the BA course. A random sequence was generated using the “RANDBETWEEN” function in MS Excel to determine which participant’s sessions were to be evaluated. Of the total 38 treatment sessions, 14 (37%) were reviewed: three of Mr X’s, four of Mr Z’s and seven of Mr Y’s, using the treatment adherence checklist provided by Lejuez et al. (2011). Of 69 treatment components across 14 sessions, 67 were identified by the independent rater (97% treatment adherence).

### *Data analysis*

The data analytic plan was selected as appropriate for time series data and used a mix of structured visual analysis, from the protocol of Kratochwill et al. (2013), and statistical techniques. First, the data were evaluated for autocorrelation, which, if present, may lead to a greater chance of Type 1 error. We followed the procedure recommended by Solanas, Manolov, and Sierra (2010). The delta-recursive estimator for short data sets (i.e., less than 20 time points) was used, which was adjusted according to data series length. We applied the formula recommended by Huitema and McKean (1991) as a two-tailed test of the statistical significance of autocorrelation. In total, there were 24 baseline, treatment and maintenance phases. Autocorrelation was not calculated in six phases (five phases for Mr Z and one for Mr X) because of short phase length (only three data points in each). Of the 18 phases for which autocorrelation was calculated, there were five phases (27.8%) with significant auto-correlation: two for Mr X, two for Mr Y and one for Mr Z; and data from these phases were interpreted cautiously.

Second, the frequency of TBs within and across phases was evaluated using structured visual analysis. Six features were considered: (i) level: change in the mean score between adjacent phases; (ii) trend: the slope of best fitting straight line within phases; (iii) variability, defined by stability window  $\pm 25\%$  of the baseline median; (iv) immediacy of effect, as measured by the change in level between the last three data points in one phase and the first three in the next phase; (v) the proportion of data overlap between phases; and (vi) consistency of data patterns in similar phases. Appropriate visual analytic techniques were applied to these data features based on the recommendations of Gast and Spriggs (2014). Data in each phase were variable, with 23 of 24 phases having less than 80% of data points within the stability envelope.

Mood ratings were analysed differently to the TB data because data were collected continuously across the baseline, treatment and maintenance phases for all three tiers. These data were subject to visual analysis supported by the quasi-statistical technique of evaluating if improvement occurred that was greater than two standard deviations above the baseline average, as an indicator of clinically meaningful improvement (Manolov & Solanas, 2017).

Third, statistical analyses used the Tau-*U* statistic because it is able to demonstrate non-overlap of phases with good statistical power for small data sets (Manolov & Moeyaert, 2017). Parker, Vannest, Davis, and Sauber (2011, p. 296) demonstrated that there is a negligible effect of low to moderate levels of auto-correlation and that Tau-*U* can be effectively adjusted for unstable baseline data. Tau-*U* also provides an overall weighted index for the combination of data from all three tiers in order to establish the effectiveness of the intervention within participants. Outcome data were aggregated into weekly totals, consistent with the therapy session structure which served as the unit of measurement. Analysis was conducted using the online calculator at [www.singlecaseresearch.org](http://www.singlecaseresearch.org) Effect sizes were used to interpret the findings rather than focusing on *p* values in order to account for autocorrelation as recommended by Vannest, Peltier, and Haas (2018).

Finally, secondary and generalization measures were analysed using the Reliable Change Index (RCI; Jacobson & Truax, 1991) comparing change between each phase/treatment for each participant. The RCI was set at 1.96 using normative data derived from other studies with data from a brain-impaired sample where available (Ownsworth et al. (2008) for DASS21; Sinclair et al. (2010) for Rosenberg Self-Esteem Scale; von Steinbüchel et al. (2005) for QOLIBRI; Bogner et al. (2017) for SWLS).

## Results

Table 1 provides personal information for the three participants. TB data are displayed for each participant separately in Figures 1–3 as aggregated session-by-session weekly totals of activity; the graphed daily raw data record is displayed in Online Appendix B. Descriptive statistics and results of the Tau-*U* analyses are tabulated in Online Appendix C. Figures 1–3 also display average mood rating per week in parallel to the TB data for each participant with the baseline mean and + 2SD cut-off projected into the treatment phases. Table 2 provides average mood ratings, secondary and generalization measures for each phase.

### Case formulation

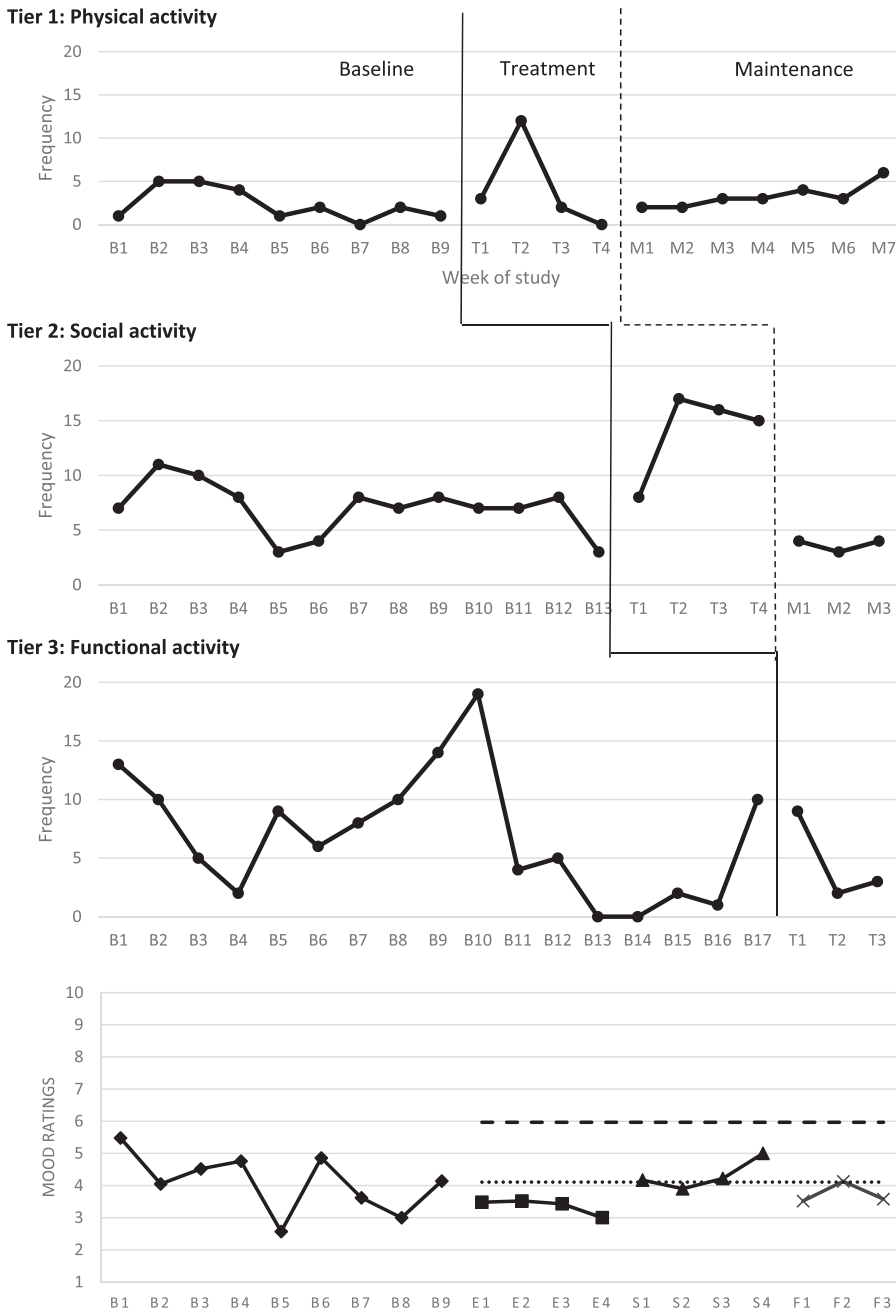
Each participant's clinical assessment was consistent with the case formulation that failure to achieve meaningful life goals served to maintain their depressed mood. We hypothesized that increasing participation in values-based activities

**Table 1.** Participant information table.

Name	"Mr X"	"Mr Y"	"Mr Z"
Age	26	46	26
Type of injury	Mild TBISpinal Cord Injury at T4GCS 13/15 at sceneBrachial plexus injury	Extremely severe TBIGCS 13/15 at sceneCT imaging abnormalities including left frontal and cerebellar subdural haemorrhages (SDH), multiple contusions in frontal lobes, skull fractures. Chest injuries.	Series of strokes as an infant
Cause of trauma	Motor accident	Motor accident	N/A
Length of PTA	Not documented	45 days	N/A
Time since injury	2 years	1 year and 3 months	25 years
Cognitive status based on review of available neuropsychological reports	Intellectual ability in average range.Attention and concentration reduced to low average.Reductions in learning tasks.Low average verbal reasoning.Executive dysfunction: literal and concrete thinking style	Slowed speed of information processing, reduced flexibility, global memory deficits, poor judgement and reduced verbal generativity. Poor insight and denial (declined further neuropsychological assessment)	Executive dysfunction including poor emotional and social perception. Distractible. Poor inhibition of incorrect responding. Perseveration.
Medications	Gabapentin, Fentanyl, Oxycodone and Paracetamol for pain;Olanzapine and Mirtzapine for mood and anxiety	Nil	Nil
Depression diagnostic status	DSM-IV-TR criteria met for Major Depressive Disorder, Single Episode, Moderate severity	DSM-IV-TR criteria met for Major Depressive Disorder, Recurrent, Moderate to Severe.DMS-IV-TR criteria met for Alcohol Dependence	DSM-IV-TR criteria met for Major Depressive Disorder, Single Episode, Mild severity
Primary symptoms of depression	Depressed moodAnhedoniaExcessive feelings of guilt and remorseLow self-esteem and poor self-image	Depressed moodAnhedoniaFeelings of worthlessness. Recurrent thoughts of suicide without a specific plan. Irritability.	Depressed moodAnhedonia
Current occupation	Unemployed	Unemployed	Unemployed
Pre-injury occupation	Self-employed tradesperson	Unemployed, had worked as a chef	Injury prior to working age however has held casual job
Level of assistance required	Drop-in support for domestic tasks and some personal hygiene	Requires prompting for appointments and planning assistance for transport	Requires supervision and prompting in social situations
Relationship status	Separated	Separated	Single
Living situation	Alone	Alone	With family

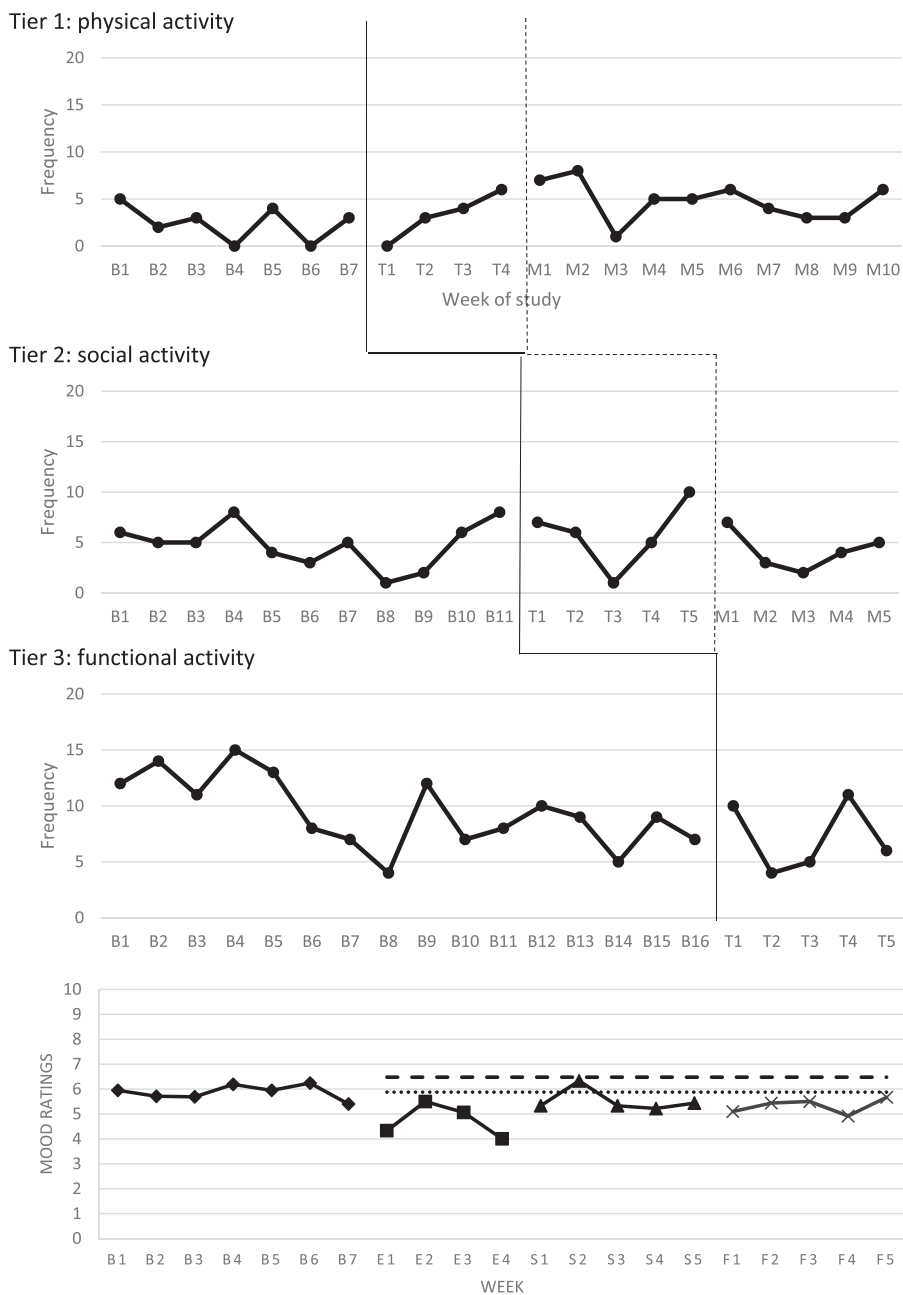
\*indicates reliable change (RCI) between current and previous phase.

^indicates reliable change (RCI) between Baseline and end of Functional treatment.



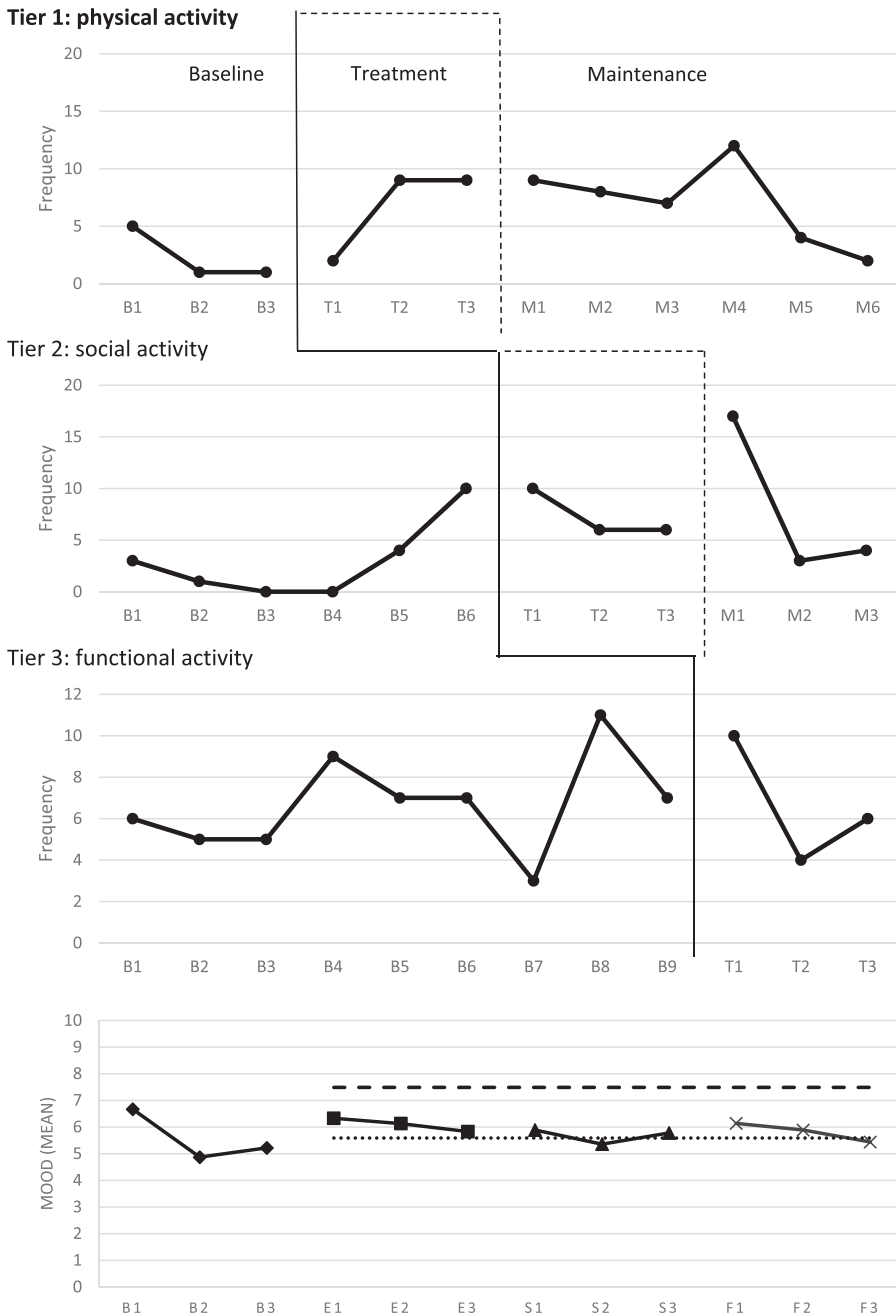
**Figure 1.** Case 1 – Mr X – frequency of activities and mean mood ratings per week. See Online Appendix B for the full graphed raw data record (daily recordings). Explanation of mood. Weeks: B = baseline, E = physical, S = social, F = functional. Projected = baseline mean projected into treatment phases. 2SD = two standard deviations above baseline mean as a test of significant change.

directed towards goals would lead to an increase in mood ratings on the DAL. Participation was affected by lack of structured time, poor planning and motivation, low self-esteem, poor self-image and reduced social networks. Weekly BA



**Figure 2.** Case 2 – Mr Y – frequency of activities and mean mood ratings per week. See Online Appendix B for the full graphed raw data record (daily recordings). Explanation of mood. Weeks: B = baseline, E = physical, S = social, F = functional. Projected = baseline mean projected into treatment phases. 2SD = two standard deviations above baseline mean as a test of significant change.

sessions identified participants’ personal values, activities based on those values, and ways to overcome obstacles to participation. Activities were scheduled in order to provide structure to the participants’ time.



**Figure 3.** Case 3 – Mr Z – frequency of activities and mean mood ratings by week. See Online Appendix B for the full graphed raw data record (daily recordings). Explanation of mood. Weeks: B = baseline, E = physical, S = social, F = functional. Projected = baseline mean projected into treatment phases. 2SD = two standard deviations above baseline mean as a test of significant change.

**Case 1:**

Mr X was a 26-year-old man, separated from his partner, who had sustained a mild TBI and a spinal cord injury in a motorcycle accident two years previously.

**Table 2.** Mood ratings, secondary and generalization measures.

	Baseline	Treatment tier 1: Physical	Treatment tier 2: Social	Treatment tier 3: Functional
Mood ratings: Mean (SD)				
Mr X	4.11 (0.93)	3.36 (0.24)	4.32 (0.47)	3.74 (0.34)
Mr Y	5.88 (0.30)	4.72 (0.68)	5.53 (0.45)	5.33 (0.31)
Mr Z	5.59 (0.95)	6.10 (0.25)	5.68 (0.28)	5.82 (0.35)
Secondary measures				
<i>DASS21 depression</i>				
Mr X	18	22	18	20
Mr Y	32	20*	20	16 <sup>^</sup>
Mr Z	22	12*	12	8 <sup>^</sup>
<i>QOLIBRI</i>				
Mr X	46	51*	57*	60* <sup>^</sup>
Mr Y	58	49*	48	62* <sup>^</sup>
Mr Z	45	45	45	49* <sup>^</sup>
<i>Rosenberg self-esteem scale</i>				
Mr X	16	14	17	18
Mr Y	21	18	19	16
Mr Z	13	15	15	14
<i>Satisfaction with life scale</i>				
Mr X	14	13	11	11
Mr Y	15	16	12	19
Mr Z	19	17	20	21

\*indicates reliable change (RCI) between current and previous phase.

<sup>^</sup>indicates reliable change (RCI) between Baseline and end of Functional treatment.

He mobilized in a powered wheelchair and could transfer independently. Professional carers helped for a few hours every second day with physically demanding domestic activities, such as maintaining his small garden. Prior to the accident he was self-employed in a manual occupation but had not worked since his injury. He spent most time alone, watching TV. Mr X's depression was maintained by a loss of physical capacity, poor self-esteem and the breakdown of his marriage. The intervention attempted to increase his sense of purpose and was directed towards meaningful activity and structure.

Baseline data collection was extended for Mr X in order to consolidate monitoring procedures (he required frequent reminding to complete the DAL). Mr X's participation in the study was affected by a period of hospitalization during week 1 of treatment in tier 3.

### *Tier 1: Physical activity*

*Structured Visual Analysis:* Figure 1 displays the aggregated frequency of activities per week for all tiers. There was an increase in average physical activities per week from baseline ( $M = 2.33$ ,  $SD = 1.87$ ) to treatment phase ( $M = 4.25$ ,  $SD = 5.32$ ) with a slight reduction in the maintenance phase ( $M = 3.29$ ,  $SD = 1.38$ ). The trend of the baseline was decelerating and with greater deceleration during the treatment phase, although this levelled to zero-celerating in the maintenance phase. There was an immediate effect of change from baseline to treatment (+2 activities in a week) and from treatment to maintenance (+2 activities in a week). There was a high degree of overlapping data between baseline and treatment, and treatment and maintenance phases.



*Statistical analysis:* Tau-*U* effect size calculations for the contrast between baseline and treatment indicated negligible effect in favour of treatment with a wide confidence interval ( $ES = 0.14$ ,  $90\%CI = -0.45-0.73$ ,  $p = 0.70$ ). There was a similar finding for the contrast between treatment and maintenance ( $ES = 0.18$ ,  $90\%CI = -0.44-0.80$ ,  $p = 0.64$ ).

### **Tier 2: Social activity**

*Structured visual analysis:* There was an increase in mean frequency of social activities from baseline ( $M = 7.0$ ,  $SD = 2.42$ ) to treatment ( $M = 14.0$ ,  $SD = 4.08$ ) and a reduction to below baseline during the maintenance phase ( $M = 3.67$ ,  $SD = 0.58$ ). Trend of the baseline was decelerating but was accelerating during treatment and was zero-celerating during maintenance. There was an immediate effect of treatment (+ 5 activities in a week) and an immediate reduction at the onset of the maintenance phase (-12 activities in a week). There was only one data point of overlap between baseline and treatment phases, and no overlap between treatment and maintenance.

*Statistical analysis:* There was a significant difference on Tau-*U* between baseline and treatment phases ( $ES = 0.88$ ,  $90\%CI = 0.29-1$ ,  $p = 0.01$ ) and treatment versus maintenance phase ( $ES = -1$ ,  $90\%CI = -1 - -0.23$ ,  $p = 0.03$ ), however the latter analysis is interpreted more cautiously because of significantly autocorrelated data in the maintenance phase.

### **Tier 3: Functional activity**

*Structured visual analysis:* There was a decrease in mean weekly functional activities from baseline ( $M = 6.94$ ,  $SD = .38$ ) to treatment ( $M = 4.67$ ,  $SD = 3.79$ ). The trend was decelerating in baseline with a greater rate of deceleration in treatment. The immediate effect was a slight reduction in the first week of the treatment phase (-1 weekly activities). There was a high degree of overlapping data between baseline and treatment.

*Statistical analysis:* There was significant autocorrelation within the baseline data and autocorrelation was not calculated due to the short length of the treatment phase. There were no significant findings on Tau-*U* ( $ES = -0.24$ ,  $90\%CI = -0.85-0.37$ ,  $p = 0.52$ ).

### **Overall response to treatment**

Consideration of consistency of data in similar phases relied upon analysis of baseline stability and the effect on level and trend when the treatment was introduced. For Mr X none of the baseline phases were stable. Mr X did show an immediate increase in participation upon introduction of treatment in tiers 1 (physical) and 2 (social) but not tier 3 (functional).

The Tau-*U* weighted average response to treatment across tiers indicated a moderate change from baseline to treatment but this was not significant ( $ES = 0.28$ ,  $90\%CI = -0.06-0.62$ ,  $p = 0.17$ ). Comparison between treatment and

maintenance phases was not conducted because there was no maintenance phase in Tier 3.

### *Mood and pain ratings*

Mr X demonstrated variations in mood during the baseline phase such that his average ratings fluctuated between 5.5 and 2.6. His mood decreased to below baseline levels when the first treatment (physical) was implemented and then returned to the baseline average. Pain ratings remained stable throughout the study. Mean scores for pain ratings (with standard deviations in parentheses) were: baseline = 3.68 (0.47), physical = 3.70 (0.36), social = 3.50 (0.48) and functional = 3.31 (0.53).

### *Secondary and generalization measures*

Descriptive statistics for secondary and generalization measures for all participants are displayed in [Table 2](#). RCI showed improvements in the QOLIBRI at the introduction of each treatment phase. There was no significant change with other measures.

### *Case 2:*

Mr Y was a 46-year-old man, separated from his partner, who suffered a TBI in a motor vehicle accident. Fifteen months post-accident Mr Y presented as depressed, with little motivation and tendency towards heavy drinking. His depression was maintained by relationship breakdown which led to changes in his social role. The intervention specifically targeted the problem of social isolation and this directly informed the choice of TB directed towards increasing social contact and identifying personally meaningful activities.

Mr Y's participation in the study was compromised by periods of approximately a week at a time when he was uncontactable and during which he engaged in heavy alcohol use. Weekly data for the performance of activities is displayed for each tier, along with concurrent mood data, in [Figure 2](#). Where there was missing data it was assumed that no TBs had occurred and a score of zero was allocated. This occurred in parts of week 1–2 of treatment in tier 1 and weeks 3–4 of treatment in tier 2. These periods are indicated in [Online Appendix B](#), [Figures 4 and 5](#).

### *Tier 1: Physical activity*

*Structured visual analysis:* There was an increase in mean weekly frequency of activities from baseline ( $M = 2.43$ ,  $SD = 1.90$ ) to treatment ( $M = 3.25$ ,  $SD = 2.50$ ) to maintenance phases ( $M = 4.80$ ,  $SD = 2.10$ ). The baseline trend was decelerating with accelerating trends in treatment and maintenance phases. There was a counter-therapeutic effect upon the introduction of treatment (–3 activities

in the first week) and a slight increase upon the introduction of the maintenance phase. There was a high degree of overlap between phases.

*Statistical analysis:* There was no significant difference in phase contrasts on Tau-U (Baseline versus treatment  $ES = 0.25$ ,  $90\%CI = -0.37-0.87$ ,  $p = 0.51$ ; treatment versus maintenance  $ES = 0.38$ ,  $90\%CI = -0.21-0.96$ ,  $p = 0.29$ ). There was significant autocorrelation affecting the treatment phase.

### **Tier 2: Social activity**

*Structured visual analysis:* The mean frequency of social activity did increase slightly from baseline ( $M = 4.82$ ,  $SD = 2.23$ ) to treatment ( $M = 5.80$ ,  $SD = 3.27$ ) but reduced in the maintenance phase ( $M = 4.20$ ,  $SD = 1.92$ ). In baseline there was a decelerating trend with no clear trend in treatment and a slight acceleration in maintenance. In relation to immediacy of effect, there was a slight drop ( $-1$  activity in a week) in social activities upon the commencement of treatment and a larger drop ( $-3$  activities in a week) at the start of the maintenance phase. There was almost complete overlap of data between phases.

*Statistical analysis:* There was no significant difference in phase contrasts on Tau-U (Baseline versus treatment  $ES = 0.24$ ,  $90\%CI = -0.29-0.76$ ,  $p = 0.46$ ; treatment versus maintenance  $ES = -0.36$ ,  $90\%CI = -0.99-0.27$ ,  $p = 0.35$ ).

### **Tier 3: Functional activity**

*Structured visual analysis:* There was a reduction in activity participation from the baseline phase ( $M = 9.44$ ,  $SD = 3.18$ ) to treatment phase ( $M = 7.20$ ,  $SD = 3.11$ ). The baseline trend was decelerating with no discernible trend during treatment. There was an immediate effect ( $+3$  activities) but also extensive data overlap.

*Statistical analysis:* There was significant autocorrelation in the baseline phase. There was no significant difference for Tau-U comparison of baseline and treatment ( $ES = 0.2$ ,  $90\%CI = -0.30-0.70$ ,  $p = 0.50$ ).

*Overall response to treatment:* The Tau-U weighted average response to treatment across tiers was not significant (Tau-U = 0.22,  $90\%CI = -0.15-0.61$ ,  $p = 0.24$ ).

### **Mood ratings**

Mr Y's mood ratings were fairly consistent through the study with his average mood rating during baseline just below 6/10, and average mood ratings during treatment phases in each tier lower than this. His mood did not improve above the  $+2SD$  level.

### **Secondary and generalization measures**

There was a significant decrease in DASS21 depression ratings from baseline to physical activity treatment, as demonstrated by RCI. The reduced level was then maintained during the social and functional treatments. There was a significant reduction in QOLIBRI when physical activity treatment began, but this

rebounded to be significantly above baseline levels according to RCI at the conclusion of tier 3 treatment.

### Case 3:

Mr Z was a 26-year-old single man who suffered a series of strokes as an infant. He developed with a range of cognitive deficits relating to executive function and social competence. He had a poor grasp of social convention and his problematic behaviours included poor social perception leading to him not recognizing social cues, a tendency towards becoming overly emotional, disclosing too much personal information, repeating stories and invading the personal space of others. Mr Z presented with flattened affect and reported low mood. He was largely inactive, with poor self-esteem. His depression was maintained by lack of goal attainment and social isolation. TBs were directed towards increasing social contact and breaking down long-term tasks into short-term activities.

#### Tier 1: Physical activity

*Structured visual analysis:* Physical activity increased from baseline ( $M = 2.33$ ,  $SD = 2.31$ ) to treatment ( $M = 6.67$ ,  $SD = 4.04$ ) and maintenance ( $M = 7.00$ ,  $SD = 3.58$ ). There was a decelerating trend during the baseline, an accelerating trend in treatment phase with a decelerating trend during maintenance. The immediacy of effect was small (+1 weekly activity) for the introduction of treatment, and nil for the introduction of maintenance phase. There was some overlapping data due to a higher than average level of activity at the beginning of the baseline phase.

*Statistical analysis:* There were no significant findings for Tau- $U$  contrasts. Baseline versus treatment effect was moderate-to-strong but with a wide confidence interval ( $ES = 0.78$ ,  $90\%CI = 0.06-1.00$ ,  $p = 0.13$ ); there was negligible effect for treatment versus maintenance ( $ES = -0.06$ ,  $90\%CI = -0.66-0.65$ ,  $p = 0.90$ ).

#### Tier 2: Social activity

*Structured visual analysis:* From baseline ( $M = 3.00$ ,  $SD = 3.79$ ) there was increased participation in social activity during the treatment phase ( $M = 7.33$ ,  $SD = 2.31$ ) and this was continued into the maintenance phase, albeit with more variability ( $M = 8.00$ ,  $SD = 7.81$ ). There was an accelerating trend during the baseline phase, with deceleration during treatment and maintenance phases. There was no immediate effect of the introduction of treatment, but a large effect of the introduction of the maintenance phase (+11 activities per week) probably because social activities take time to arrange whereas other types of activities can be more spontaneous. There was only one point of overlap between baseline and treatment, but considerable overlap between treatment and maintenance phases.

*Statistical analysis:* There was an accelerating trend in participation during the baseline phase, which was significantly autocorrelated. Tau-*U* was approaching significance for the baseline versus treatment contrast with a moderate-to-strong effect size ( $ES = 0.72$ ,  $90\%CI = 0.01-1.0$ ,  $p = 0.09$ ). The treatment versus maintenance contrast was not significant with a small, negative effect ( $ES = -0.33$ ,  $90\%CI = -1-0.50$ ,  $p = 0.51$ ).

### *Tier 3: Functional activity*

*Structured visual analysis:* the mean participation did not change from baseline ( $M = 6.67$ ,  $SD = 2.35$ ) to treatment ( $M = 6.67$ ,  $SD = 3.05$ ) phases. There was no discernible trend during baseline and a decelerating trend during the treatment phase. There was an immediate effect of increase participation at the start of the treatment phase (+3 activities per week). There was high overlap between the baseline and treatment phases.

*Statistical analysis:* there were no significant findings on Tau-*U* with negligible effect and a wide confidence interval ( $ES = -0.07$ ,  $90\%CI = -0.73-0.59$ ,  $p = 0.85$ ).

*Overall response to treatment:* There was no significant effect of treatment across the three tiers. The effect size was moderate ( $ES = 0.42$ ,  $90\%CI = 0.00-0.83$ ,  $p = 0.10$ ).

### *Mood ratings*

There was little change in average weekly mood rating during the study and average mood ratings remained below the + 2SD cut-off.

### *Secondary and generalization measures*

There was a significant drop in DASS21 depression symptoms at the end of the physical activity treatment and this was maintained through to the end of the study. There was a significant improvement in QOLIBRI during the functional activity treatment.

## **Discussion**

This study evaluated the effectiveness of BA for treating activity participation and mood in people who were depressed following brain injury. In these three cases there was little evidence in support of BA increasing participation across three TBs. However, there was evidence, from structured visual analysis and statistical analysis, in support of BA for some activities (physical and social) with some participants (Mr X and Mr Z). The strongest demonstrated positive effect was for Mr X's participation in social activities. While the other participants demonstrated a higher average weekly participation in physical and social activities during the relevant treatment phases, this was within the context of an unacceptable degree of variability in almost every phase of the study. Importantly, there was no clear pattern with maintenance phases and therefore it was not possible to

draw conclusions about whether the treatment was effective after the focus shifted to a new TB.

Behavioural activation was chosen as an intervention for people with depression following brain injury and was implemented with very high (97%) treatment adherence. BA lent itself to a multiple-baseline design because it is directed towards increasing target behaviours and utilizing repeatable measures. There are some possible explanations why BA was not found to be effective for the three participants. Two participants (Mr X and Mr Y) were adversely affected by health and personal relationship events which affected their participation. Mr Y was unable to overcome the problem of financial constraints and living in an isolated location. Like another recent study by our group, extraneous variables appeared to affect participation (Tate, Wakim, Sigmundsdottir, & Longley, 2018) and additional resources might have helped. Introducing new activities required significant planning and when we identified recurring weekly activities, such as local fitness training or social groups that included transport, participation was easier.

The findings of this study suggest that BA evaluated here does not go far enough in addressing unwanted thoughts and feelings underpinning depression. During the study Mr X commented, "I'm doing all these things but I'm still not feeling any better" and inferred that intervention was not meeting his needs. There is recent evidence of the effectiveness of psychological interventions when treatment is conducted over longer periods and is combined with other interventions. Ponsford et al. (2016) conducted an RCT of cognitive-behavioural therapy with either motivational interviewing or non-directive counselling. The treatment was conducted over 12 weeks but there were three booster sessions applied between 21- and 30-weeks post-baseline. The data indicated that DASS depression scale scores were relatively stable from the conclusion of the initial 12-week treatment until the 21-week timepoint and it was not until the 30-week timepoint that there was significant difference between the treatment groups and the wait-list control. This was not influenced by therapy type but rather by the extra sessions. The current study may have benefitted from additional therapeutic contact not just because of the Ponsford et al. findings, but also because treatment was disrupted for two of the participants (Mr X and Mr Y) and because it took some time to organize new routines that would have enhanced participation.

Balán, Lejuez, Hoffer, and Blanco (2016) acknowledge that BA places heavy "out-of-session" demands on patients and that it depends greatly on patient motivation, organization and self-prompting, which may be problematic for people with brain impairment. The three participants were selected because of their cognitive profiles and this included impairments in planning, initiating and completing activities. In the case of Mr Z, who had strokes in infancy, there were global impairments in functioning and a lack of experience in planning activities independently. Participants were already using electronic

devices to record responses to the DAL and so it may have been helpful to deliver messages to their device. Wong, Sinclair, Seabrook, McKay, and Ponsford (2017) found that people with TBI often had smartphones and recommended clinicians support the use of such devices to increase independence. Furthermore, Hart and Vaccaro (2017) found that delivering text messages with “goal-related implementation intentions” increased participation for people with TBI. It is possible that had the current study used electronic devices to prompt activity and deliver relevant messages this might have increased participation.

We evaluated the methodological quality of this study using the Risk of Bias in N-of-1 Trials (RoBiNT) scale (Tate et al., 2013a) (see Online Appendix D). The total score was 21/30. It scored a total of 6/14 for the internal validity subscale losing points because of (i) lack of randomization of the onset of treatment in a multiple-baseline design, (ii) lack of blinding of participants and practitioners which was not possible because of the nature of the intervention, and (iii) lack of blinding of assessors which was not possible because of the use of self-report data. Similarly, (iv) it was not possible to award points for inter-observer agreement because this relied on self-report data. The study scored 15/16 for the external validity and interpretation subscale losing one point for replication. In a multiple-baseline design the experiment would need to be replicated with three additional participants (i.e., total of four participants) in order to score full points for this item.

The Internal Validity subscale score was consistent with moderate methodological rigour, according to the RoBiNT algorithm (Perdices, Tate, & Rosenkoetter, 2019). However, the score does highlight methodological problems because of the reliance on self-report data. Choi et al. (2019) conducted a large meta-analysis of general population samples and found that there was a causal, protective relationship between levels of physical exercise and the development of major depressive disorder when based on objective data from wrist-worn devices such as activity trackers and “smart” watches (meta-analytic subsample  $n = 91,084$ ) but not when based on self-report data (meta-analytic subsample  $n = 377,234$ ). Self-report measures of activity might be affected by mood states and cognitive biases that also affect mental health. Using wrist-worn devices would have increased the accuracy of the recording in the current study and possibly led to different findings for activity participation in the physical activity tiers. Use of objective data collection methods would have increased the methodological quality of the study and might have led to different findings. For instance, Lane-Brown and Tate (2010) provide an example of objective rating of functional activities by taking photographs of a participant’s bedroom which were then rated for “tidiness” by two clinicians.

In spite of the nonsignificant results, this SCED study provides a model for the evaluation of clinical cases that practitioners can use in every day clinical practice. By using a web-based daily activity log (DAL) we were able to track the daily progress of the participants which fits within the Model to Assess

Treatment Effect (Tate, Taylor, & Aird, 2013b). The DAL was repeated three times a day to lessen the burden of memory, however this differed from how such data are usually collected in the BA manual and might have changed the utility of the measurement. It is also possible that the introduction of monitoring or the enrolment in the study, and the increased contact with researchers, changed participation and mood and that this could have affected the baseline data. Jamieson et al. (2017) evaluated the use of a smartwatch for people with ABI and found lower participation during the reversal phase than the baseline phase. This suggested that the initial baseline response could have reflected an improvement in the TB due to enrolment in the study and its accompanying data collection procedures.

In summary, we did not find positive results overall in favour of BA increasing activity participation or mood, although there was some evidence regarding increased social activities in one case. Participation in the study appeared to be affected by extraneous variables and clinicians need to plan for the impact of these factors in delivering treatment. The study provides an example of how clinicians can conduct continuous evaluations of treatment using online tools.

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## Appendices

Appendix A: Table of treatment sessions

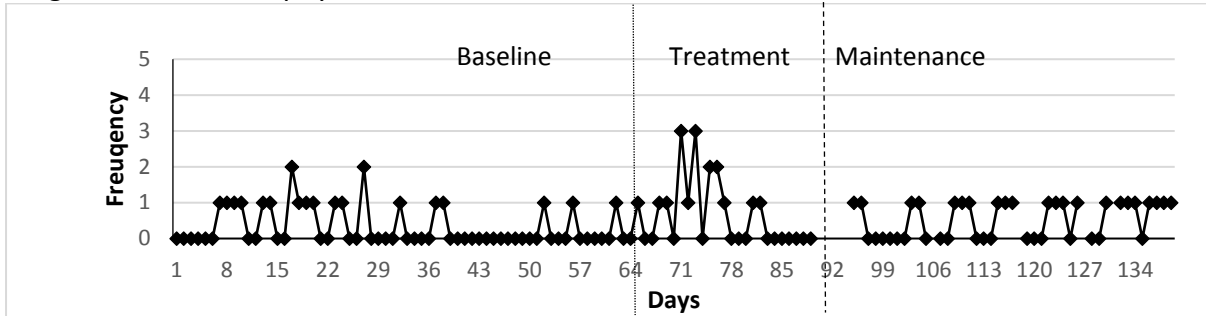
<b>Session number</b>	<b>Participants</b>	<b>Key elements</b>
1	All	Introduction Discussion of depression Introduction to treatment rationale Introduction to daily monitoring Important points about the structure of treatment Assignments: Daily monitoring
2	All	Daily monitoring review Treatment rationale – review assignment Important points about the structure of treatment – review assignment Complete the Life Areas, Values, Activities Inventory Assignments: Daily monitoring; review the Life Areas, Values, Activities Inventory
Target behaviour: physical activities		
3	All	Review daily monitoring Review the Life Areas, Values, Activities Inventory Activity selection and planning with focus on physical activities Assignments: Daily monitoring; undertake planned physical activities
4	All	Review daily monitoring Activity planning for physical activities Assignments: Daily monitoring; undertake planned physical activities
5	All	Review daily monitoring Introduce activity assistance contracts Plan daily activities for the upcoming week with focus on physical exercise Assignments: Daily monitoring; undertake planned physical activities; complete contracts
5a	Mr X and Mr Y only	Review daily monitoring Review activity assistance contracts Plan daily activities for the upcoming week with focus on physical exercises Assignments: Daily monitoring; undertake planned physical activities
Target behaviour: social activities		
6	All	Review daily monitoring Review Life Areas, Values, Activities Inventory Activity selection and planning with focus on social activities

		Assignments: Daily monitoring; undertake planned social activities
7	All	Review daily monitoring Review activity selection and ranking Plan daily activities for the upcoming week with focus on social activities Assignments: Daily monitoring; undertake planned social activities
8	All	Review daily monitoring Contracts: concept review and edit Plan daily activities for the upcoming week with focus on social activities Assignments: Daily monitoring; undertake planned social activities
8a	Mr X and Mr Y only	Review daily monitoring Plan daily activities for the upcoming week with focus on social activities Assignments: Daily monitoring; undertake planned social activities
Target behaviour functional independence tasks		
9	All	Review daily monitoring Review Life Areas, Values, Activities Inventory Activity selection and planning with focus on functional independence tasks Assignments: Daily monitoring; undertake planned functional independence tasks
10	All	Review daily monitoring Review activity selection and ranking Plan daily activities for the upcoming week with focus on functional independence tasks Assignments: Daily monitoring; undertake planned functional independence tasks
10a	Mr Y only	Review daily monitoring Contracts: concept review and edit Plan daily activities for the upcoming week with focus on functional independence tasks Assignments: Daily monitoring; undertake planned functional independence tasks Prepare for termination
10b	Mr X and Mr Y only	Review daily monitoring Prepare for termination

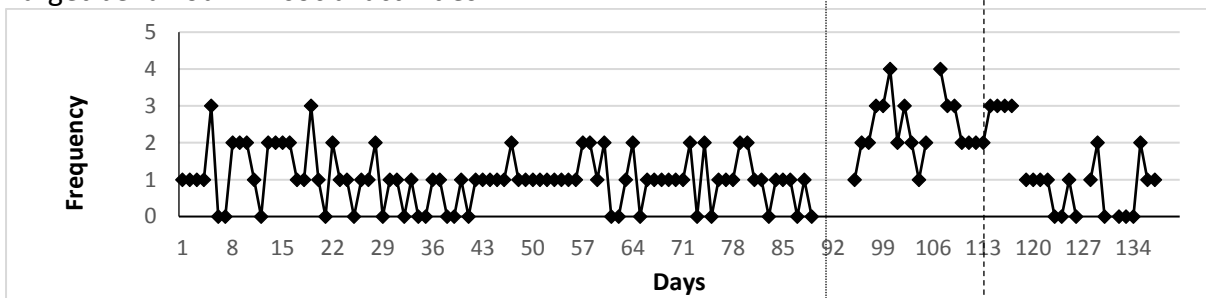
Appendix B: Raw data record for activity participation and mood

Figure 1: Activity data for Mr X

Target behaviour 1 – physical activities



Target behaviour 2 – social activities



Target behaviour 3 – domestic activities (self-rated)

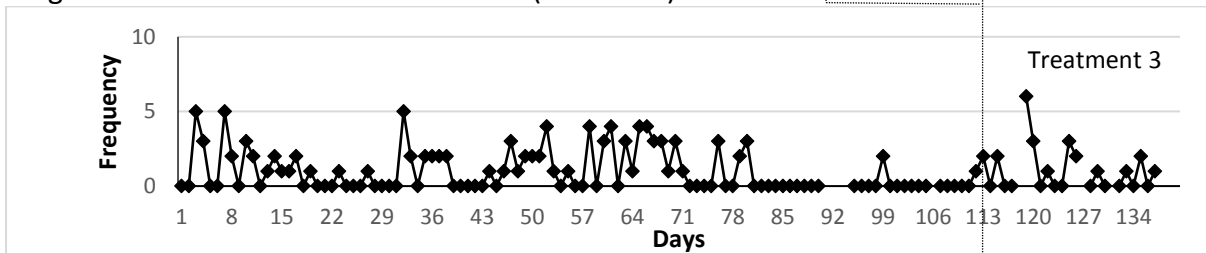


Figure 2: Mood ratings made three times a day by Mr X

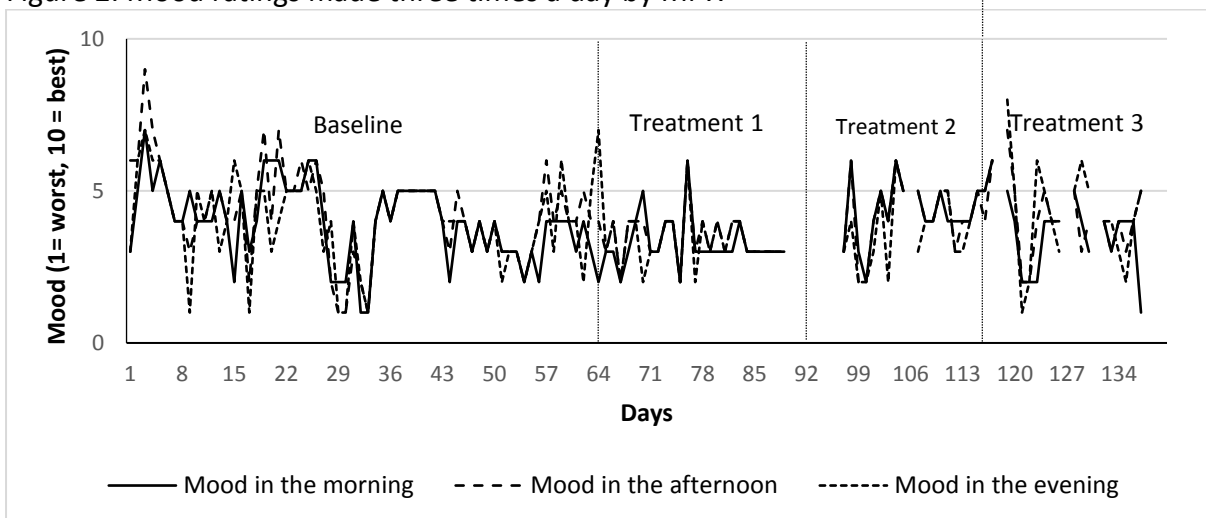


Figure 3: Pain ratings made three times a day by Mr X

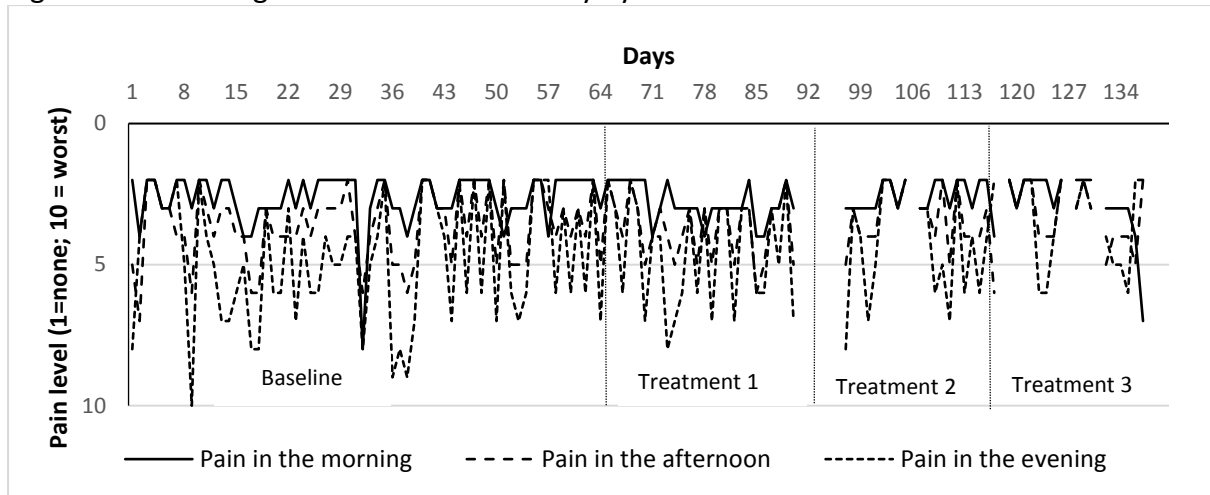
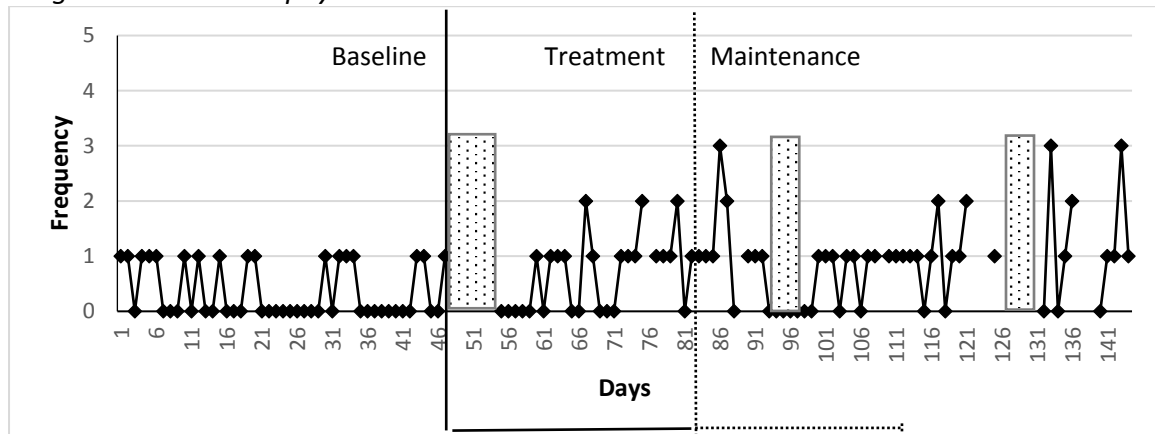
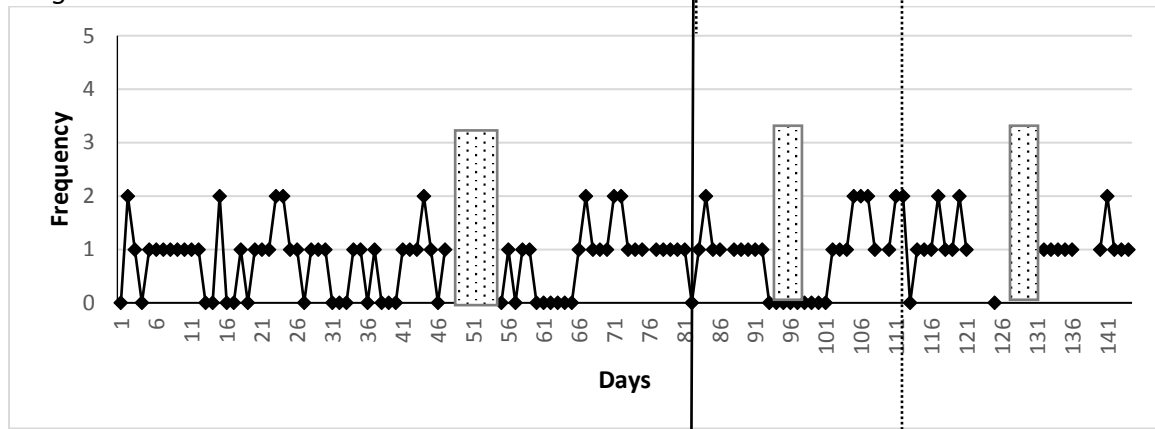


Figure 4: Activity data for Mr Y  
 Target behaviour 1 – physical activities



Target behaviour 2 – social activities



Target behaviour 3 – domestic activities

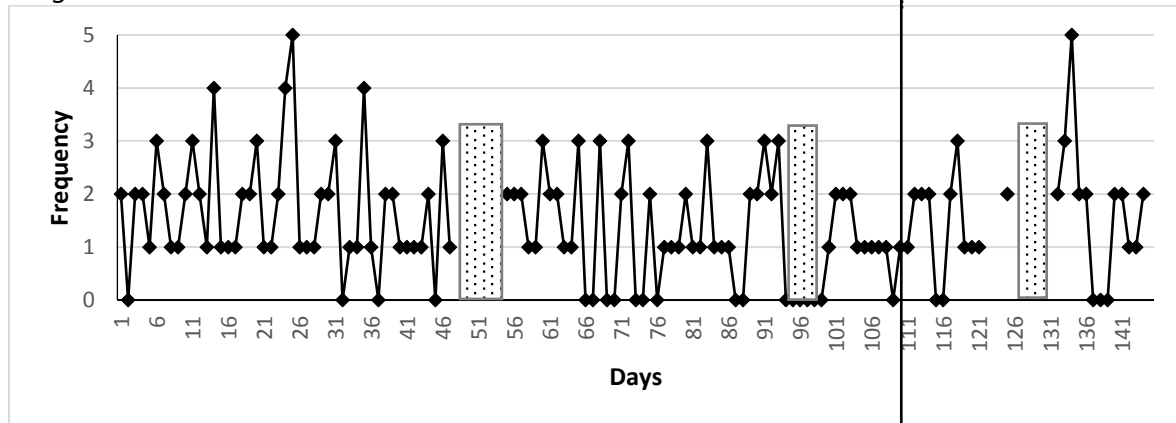




Figure 5: Mood ratings made three times a day by Mr Y

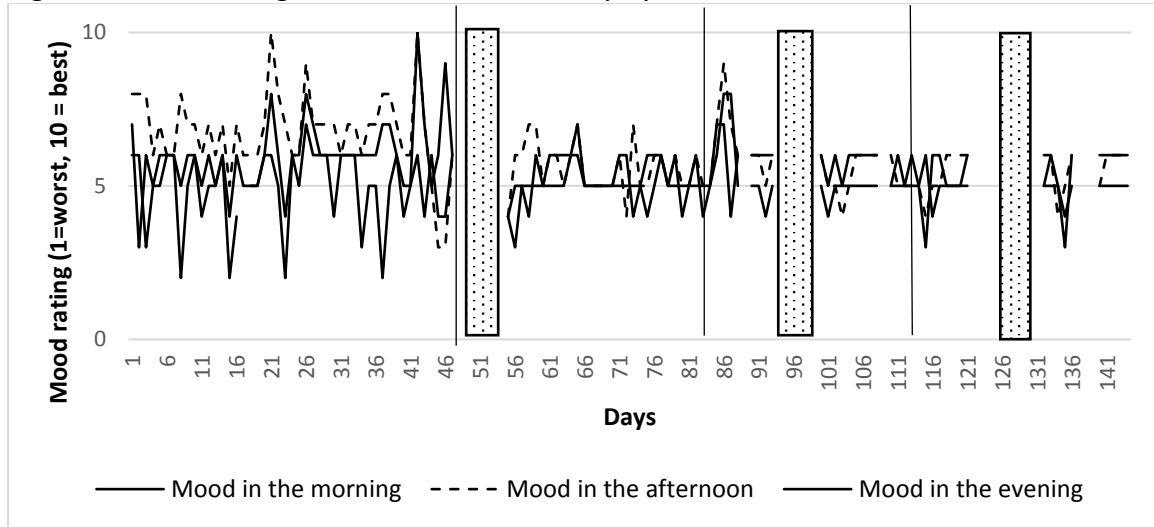
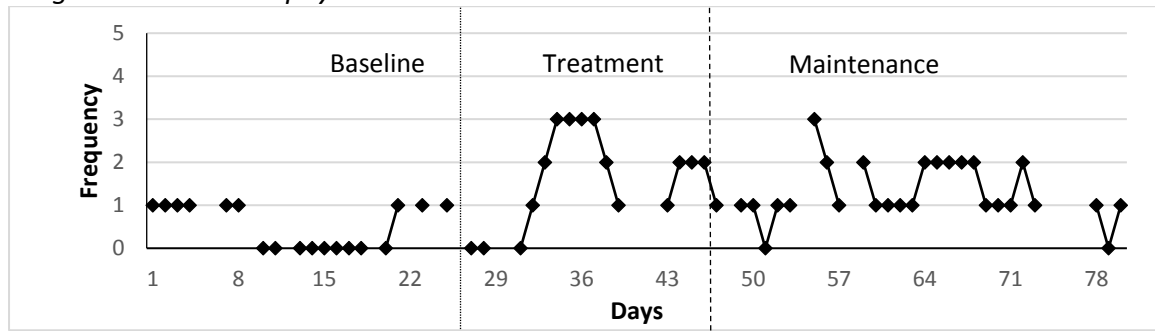
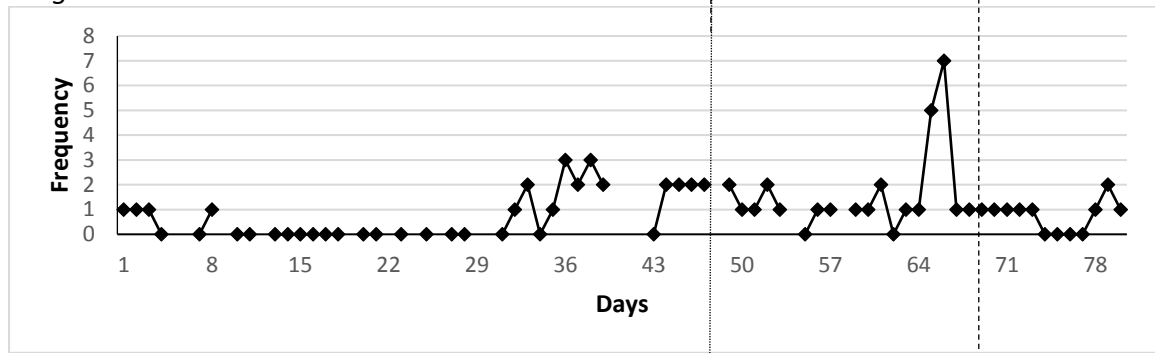


Figure 6: Activity data for Mr Z

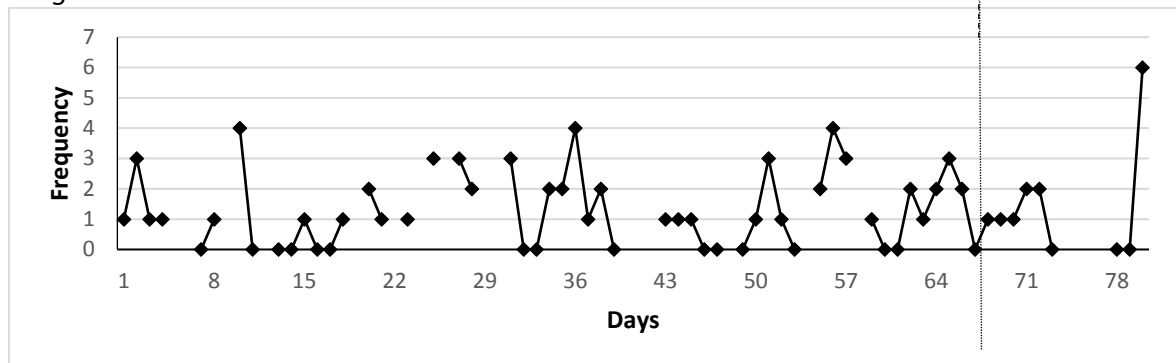
Target behaviour 1 – physical activities



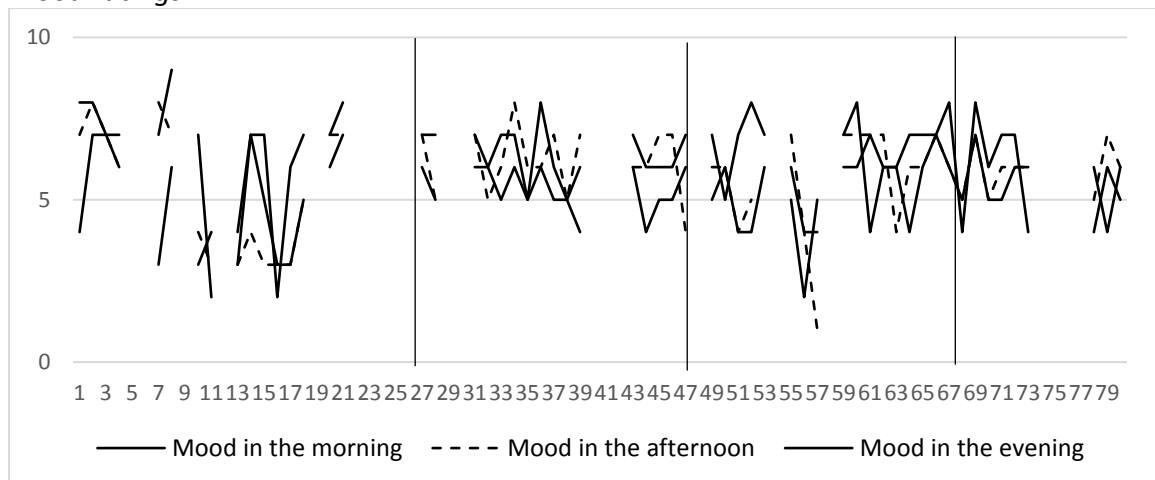
Target behaviour 2 – social activities



Target behaviour 3 – domestic activities



Mood ratings



Appendix C: Descriptive statistics and Tau-*U* analyses for target behaviours

Frequency of target behaviours per week					
Participant	Mean (SD)			Tau-U: z (ES) p 90% CI	
	Baseline phase (BL)	Treatment phase (TM)	Maintenance phase (MT)	BL vs TM	TM vs MT
<b>Case 1: Mr X</b>					
Tier 1: Physical	2.33 (1.87)	4.25 (5.32)	3.29 (1.38)	0.39 (0.14) <i>p</i> = 0.70 -0.45 – 0.73	0.47 (0.18) <i>p</i> = 0.64 -0.44 – 0.80
Tier 2: Social	7.00 (2.42)	14.00 (4.08)	3.67 (0.58)	2.49 (0.85) <i>p</i> = 0.01* 0.29 – 1	-2.12 (-1.00) <i>p</i> = 0.03* -1 – -0.23
Tier 3: Functional	6.94 (5.38)	4.67 (3.79)	-	-0.64 (-0.24) <i>p</i> = 0.52 -0.85 – 0.37	-
Weighted Tau-U				1.38 (0.28) <i>p</i> = 0.17 -0.06 – 0.62	-
<b>Case 2: Mr Y</b>					
Tier 1: Physical	2.43 (1.90)	3.25 (2.50)	4.80 (2.10)	0.66 (0.25) <i>p</i> = 0.51 -0.37 – 0.87	1.06 (0.38) <i>p</i> = 0.29 -0.21 – 0.96
Tier 2: Social	4.82 (2.23)	5.80 (3.27)	4.20 (1.92)	0.74 (0.24) <i>p</i> = 0.46 -0.29 – 0.76	-0.94 (-0.36) <i>p</i> = 0.35 -0.99 – 0.27
Tier 3: Functional	9.44 (3.18)	7.20 (3.11)	-	0.66 (0.2) <i>p</i> = 0.50 -0.30 – 0.70	-
Weighted Tau-U				1.17 (0.23) <i>p</i> = 0.24 -0.15 – 0.61	-
<b>Case 3: Mr Z</b>					
Tier 1: Physical	2.33 (2.31)	6.67 (4.04)	7.00 (3.58)	1.53 (0.78) <i>p</i> = 0.13 0.06 – 1.0	-0.13 (-0.06) <i>p</i> = 0.90 -0.76 – 0.65
Tier 2: Social	3.00 (3.79)	7.33 (2.31)	8.00 (7.81)	1.68 (0.72) <i>p</i> = 0.09 0.01 – 1.0	-0.65 (-0.33) <i>p</i> = 0.51 -1 – 0.50
Tier 3: Functional	6.67 (2.35)	6.67 (3.05)	-	-0.18 (-0.07) <i>p</i> = 0.85 -0.73 – 0.59	-
Weighted Tau-U				1.64 (0.42) <i>p</i> = 0.10 -0.00 – 0.83	-

\* *p* < 0.05

Appendix D: Scores on the Risk of Bias in *N*-of-1 Trials (RoBiNT) Scale

Item	Descriptor	Score (range 0-2); justification
<i>Internal validity subscale</i>		
1	Design	2: design was an MBD across behaviours with three opportunities to examine the experimental effect. Each of the three cases contained three tiers, with baseline-treatment-maintenance phases for two tiers, and baseline-treatment phases for the third tier.
2	Randomisation	0: although the order of treatment tiers was randomly generated by computer, the onset of treatments was not randomised.
3	Sampling	2: there was up to 140 data points presented in the raw data record (in Online Appendix B) with a minimum of 9 data points per phase.
4	Blind participant/practitioner	0: blinding of practitioners and participants was not possible due to the nature of the intervention.
5	Blind assessors	0: self-report measures were used for the target behaviours; therefore, it was not possible to have blinded assessors.
6	Inter-observer agreement	0: an independent rater, blind to the treatment conditions extracted data for all participants and across all tiers and found kappa = 0.65, to determine whether the entry in the DAL qualified as an activity and which target behaviour it should be classified into. However, this is awarded zero points because data were self-report.
7	Treatment adherence	2: adherence was determined by (a) an independent rater, using (b) the session outline of the BA manual, who reviewed video and audio-recordings of (c) > 20% of data (actually 37%), and adherence to all treatment components (d) was 97%.

<i>External validity and interpretation subscale</i>		
8	Baseline characteristics	2: basic biographical details of participants were provided including injury details. In each case, for each target behaviour, a case formulation was provided.
9	Setting	2: There was a description of the treatment locations and detailed information regarding the room layout and recording equipment.
10	Target behaviour	2: Target behaviours are identified and operationally defined in precise terms, using codes from the International classification of functioning, disability and health (ICF). This included examples of behaviours that were NOT to be coded as target behaviours. The method of recording the target behaviours is provided.
11	Intervention	2: The content of sessions is described in Appendix A. Details of the delivery including modifications for the study are provided within the body of the manuscript.
12	Raw data record	2: This is provided for observation period of the study in Online Appendix B.
13	Data analysis	2: data were subject to structured visual analysis as per accepted SCED protocols and statistical analyses were applied with justification from best-practice guidelines.
14	Replication	1: direct inter-subject replications (original + 2)
15	Generalisation	2: a priori specified generalisations measures were reported before, during and after the interventions across all tiers and participants.

Total score: 21/30; internal validity: 6/14; external validity and interpretation: 15/16

Note: MBD = multiple-baseline design

## CHAPTER 6

### *Overall Discussion and Conclusions to the Thesis*

## **6.1 Overview of thesis**

In his seminal article “Disordered mind, wounded soul: the emerging role of psychotherapy in rehabilitation after brain injury”, Prigatano (1991) asked why the potential role of psychological therapies had gone unrecognised in rehabilitation after TBI. Prigatano posited that it was because of the assumption that TBI patients could not benefit from psychological therapies because of their “permanent cognitive, linguistic, and affective disturbances” (p. 2). Fast forwarding almost 30 years to the present day and clinicians are conducting psychological interventions, but questions remain about the applicability of these interventions for people with TBI.

This thesis aimed to determine whether non-pharmacological interventions were applicable and could help depression that occurs after TBI. In order to ascertain the scope of the current evidence for interventions, a Cochrane systematic review was conducted of the available literature (Gertler, Tate, & Cameron, 2015; Chapter 2, section 1). A search was conducted up to February 2015 for RCTs of people with TBI who met clinical criteria for a diagnosis of depression or exceeded a clinical cut-off of depression symptoms. Participants must have been engaged in a treatment relevant to depression symptoms. A comprehensive database search yielded more than 2,000 records and this was combined with a hand search of more than 14,000 records, as well as a search of grey literature. When irrelevant records were excluded this left 28 full-text articles which were assessed for eligibility. Only three of these met selection criteria but an additional three studies were identified, two from searching trials registries and another from personal communication. We delayed completion of the review until these three additional studies were published so

that the review contained the most current literature. No studies were identified that included children or adolescents as participants. Of the six studies, three were evaluations of a psychological treatment compared with a no-treatment control condition. These were combined in a meta-analysis which found a very small effect in favour of treatment but was subject to a very wide confidence interval. There was variability among the three studies involving risk of bias and the overall quality of evidence (adjudged using the GRADE Working Group grades of evidence) was rated “very low.” Another study (Ashman, Cantor, Tsaousides, Spielman, & Gordon, 2014) compared two psychological treatments (CBT versus supportive psychotherapy) but did not find a significant effect in favour of either treatment. The remaining studies evaluated physical exercise and repetitive transcranial magnetic stimulation (rTMS) but the quality of evidence was such that no reliable conclusion could be drawn.

Since publication of the Cochrane review there has been ongoing interest in this topic. A further four RCTs have been published, which were described in Chapter 2, section 2. These included a replication of a previous study (Simpson, Tate, Whiting, & Cotter, 2011) evaluating CBT for hopelessness and suicidality (Brenner et al., 2018), and another study of rTMS (Hoy et al., 2019) neither of which were able to demonstrate improvements in depression in comparison with a control condition. The remaining two studies of psychological therapies demonstrated promising results with respect to reducing depression symptoms by treatment with Acceptance and Commitment Therapy (ACT; Whiting, Deane, McLeod, Ciarrochi, & Simpson, 2019) and by extending treatment with booster sessions beyond a standard course of CBT (Ponsford et al., 2016).



In the process of conducting the Cochrane review, the author became very familiar with the statistical methods and data analytic techniques of systematic reviews and meta-analyses. Using Gertler et al. (2015) as a basis we were able to explain these data analytic techniques, such as the calculation of standardised mean difference, in Gertler and Cameron (2018; see Chapter 3). The development of systematic reviews was placed in historical context. The reader was provided with insight into how to interpret the findings of Cochrane reviews and how they relate to the brain impairment literature.

Because our 2015 Cochrane review was inconclusive in terms of being able to recommend any particular intervention, the research program then turned to the problem of identifying and evaluating an intervention that could be effective for depression after TBI. In the absence of evidence-based practice recommendations, clinicians need to be able to trial interventions and determine response by individual patients in real time. In clinical practice it is common for patients to provide frequent ratings of their mood on a single-item mood scale (SIMS). This can be used in interventions to determine those components of treatment that work best for an individual. The alternative is to administer lengthier questionnaires, and these routinely refer to a period of days or weeks beforehand. For this reason, they are not appropriate instruments for capturing short-term changes. In the SIMS project (Gertler & Tate, 2020) we developed single-item mood scales that could be administered verbally or visually (see Chapter 4). We then evaluated the validity and stability of these measures. We found that SIMS showed evidence of construct validity (both discriminant and convergent/divergent) and criterion validity.

The final project, presented in Gertler and Tate (2019; Chapter 5), was a trial of a treatment to increase participation and improve mood in people with depression after TBI.

Behavioural Activation therapy was selected for people with TBI because it is behaviourally focused and should therefore place fewer demands on cognition compared with treatments that had been evaluated previously, such as CBT or Mindfulness-Based Cognitive Therapy. A single-case experimental design (SCED) study was conducted with three brain-injured patients with depression engaged in a 10- or 14-week course of behavioural activation. As per standard SCED protocol, the participants made intensive, repeated measurement using mood tracking procedures similar to the SIMS. Participants reported the frequency of activities in three domains (social, physical exercise and functional tasks). Using a multiple-baseline design, behavioural activation was modified with the aim of increasing activity participation in the three domains. Data were analysed through a combination of structured visual analysis and statistical techniques. There was a lack of evidence of an improvement in activity participation or mood, but some positive effects were found on secondary measures of depression and quality of life.

## **6.2 Answers to those clinical questions**

In Chapter 1, the author introduced the clinical questions that had inspired his program of research. The first question was “are existing interventions applicable to people with TBI?” and the second question was, “how effective are these interventions?” These questions were answered by the Cochrane review (reported in Chapter 2, section 1) which found only a handful of studies of people with depression after TBI who participated in a treatment that was applicable to depression. Some studies reported positive findings however the

quality of the evidence was very low. A meta-analysis of the studies of a psychological intervention compared with a no-treatment control found a very small effect in favour of treatment but with a very wide confidence interval. Consequently, it was not possible to recommend any therapy for use in clinical practice. In subsequent years four further studies have been published, two of which replicated the effect of previously identified studies (one of CBT and one of rTMS) without any improvement in depression symptoms. Encouragingly, two studies of novel treatment approaches, one of CBT adapted for TBI targeting concurrent anxiety symptoms and augmented by booster sessions, and another of ACT focusing on adjustment to TBI, demonstrated significant improvements on depression measures. In response to the third question, “are some interventions more effective than others?” these two new approaches appear to provide some hope of an effective treatment. In order to answer this question adequately, a future study might compare these treatments and/or use a design to identify the components of these therapies that are most effective (e.g. Hart et al., 2013; Hart & Ehde, 2015). SCEDs are eminently suitable for this purpose because they allow researchers to track response to specific treatment components.

In conducting this research program another question was “how can we best track mood to see whether treatments are working?” This question was answered by evaluating SIMS as effective mood trackers (reported in Chapter 4). SIMS are often used in clinical practice but have rarely been evaluated, particularly in neurological samples. SIMS were found to be a valid indicator of mood change after TBI that could be utilised to determine response to intervention in research and in clinical practice.

The final question was “is it possible to identify a successful intervention for depression post-TBI?” At the time of initiating the SCED study (Gertler & Tate, 2019; Chapter 5), the Cochrane review had failed to identify an effective psychological treatment. One reason for this could have been the complexity of treatments that had been evaluated and their reliance on meta-cognitive strategies such as identifying and challenging unhelpful thoughts. Therefore, a purely behavioural treatment, Behaviour Activation, was chosen to be evaluated in a SCED using a multiple-baseline design across behaviours, with replication across participants. The aim of treatment was to increase participation in three activity domains; social, physical exercise and functional tasks; and to improve mood. The study did not find significant treatment effects and several reasons were posited to account for the results. These included the impact of extraneous variables (such as the occurrence of medical emergencies) which could not be controlled; insufficient time for the participants to consolidate new activity routines; or the treatment not targeting unhelpful thoughts and feelings associated with depression. It was suggested that further research could incorporate additional treatment components in order to improve response.

### **6.3 Challenges in studying depression post-TBI and limitations of the research program**

Considering the prevalence of depression following TBI it is important to investigate treatments, however as shown by the Cochrane review (Gertler et al., 2015; Chapter 2, section 1), only one RCT (He, Yu, Yang, & Yang, 2004) was published prior to 2009. Over the past decade there has been a steady increase in RCTs but in total there are still only 10 studies of which we are aware addressing this topic, none of which apply to paediatric patients. This is most likely to be because of the challenges of conducting research with the

paediatric population rather than a lack of need and/or interest. Some of the difficulties in studying depression post-TBI are discussed below.

First, it is generally difficult to engage participants with TBI in a lengthy research project that includes an adequate baseline period, a period of treatment and then assessment throughout an appropriate follow up period. As a result, studies suffer from risk of biases due to attrition (e.g. Ashman et al., 2014; Bédard et al., 2014; Ponsford et al., 2016). This could be the result of extraneous factors that include changes in personal circumstances, difficulty accessing transport, or even the demotivation inherent in depression that contributes to reduced participation in all aspects of life. Cognitive impairments associated with TBI, such as prospective memory failures, difficulty planning, initiating and following through on activities, could prevent engagement in research (e.g. attending therapy sessions). In the SIMS study (Chapter 4) there was a significant impact of the degree of functional impairment on mood and this might not be able to be overcome. Psychological intervention can help with learning to deal with these factors, albeit perhaps only to a limited extent.

Second, various factors impact mood following TBI, which could confound the results of intervention studies. For instance, in the SIMS study (Chapter 4) we found that mood improved significantly from Time 1 to Time 2, despite no intent to manipulate mood. In the Cochrane review and two subsequent RCTs (Brenner et al., 2018; Hoy et al., 2019) the rate of improvement in mood of the treatment groups was not significantly different to the control condition because those in the control condition also improved on depression measures and additionally because of the variability in response among participants (e.g.

Bédard et al., 2014). This means that any intervention study needs to demonstrate improvement in depression symptoms over and above any natural improvement or variability, as has been demonstrated by Ponsford et al. (2016) and Whiting et al. (2019).

The effect size for the Cochrane review meta-analysis was small-to-negligible with a very wide confidence interval. It is only since the Ponsford et al. (2016) study that any RCT has shown a significant and clinically meaningful difference between treatment and control groups and the critical difference here was the follow-up of participants over a more extended timeframe than other studies, at 30 weeks post-enrolment. In the Ponsford et al. study, participants in an adapted CBT program benefitted from three “booster” sessions between 21- and 30-weeks post-enrolment.

It is still a challenge to attempt to replicate clinical practice in research programs. In clinical practice, patients are generally referred as a matter-of-course at key points in their recovery from TBI, such as when they transfer from an acute hospital setting to a rehabilitation unit, or alternatively at times of crisis. During the process of therapy, patients can experience medical or other events which impact their recoveries. This was shown during the SCED study when two participants took time away from the study, one due to an acute illness and the other when a relationship problem triggered a bout of heavy drinking. The way in which therapy was conducted in Ponsford et al. (2016) is probably the closest a group research study has come to replicating everyday clinical practice. Their study included preparatory sessions, an intensive course of therapy, followed by breaks and booster sessions. Even so, there was a substantial dropout rate such that 24 of 75 participants (32%) were lost to long-term follow up. Despite this Ponsford et al. were able to demonstrate a large effect on

DASS21-Depression scores which attests to the strength of the treatment effect for participants who completed the study. This rate of attrition can be typical of clinical practice but might also be exacerbated by the demands of being a participant in RCTs in which there is repetitive assessment and treatment is often manualised and rigid.

There are a range of other factors to consider in improving outcomes for people with depression post-TBI. Recent research by Zelencich et al. (2019, 2020) has shown that TBI-related cognitive impairments may pose a barrier to the success of CBT because of negative impacts on therapy process factors such as the development of the therapeutic alliance or the completion of homework assignments. They found that older client age, longer time since injury, better executive functioning, higher levels of homework completion and better therapist competence in reviewing homework led to better outcomes for participants with anxiety and depression post-TBI. Practising clinicians therefore have to adapt therapy modes to suit the particular cognitive profiles of people with TBI. This is often mirrored by adaptations of therapy programs by researchers interested in treatment outcomes.

Gallagher, McLeod and McMillan (2019) conducted a systematic review of modifications to CBT for people with cognitive impairments following brain injury. They found that typically CBT programs were frequently modified to include memory aids and an emphasis on socialising participants to the CBT model. Beyond these considerations, there are various other factors that have an impact on mood, and it is possible that if these are targeted it might lead to a reduction in depression symptoms. An example of this is the study by Nguyen et al. (2017) that found that an intervention to target sleep and fatigue led to an improvement in depression symptoms as measured by the Hospital Anxiety and Depression

Scale that was greater than studies specifically targeting depression (e.g. Ponsford et al., 2016).<sup>1</sup>

Finally, in conducting the behavioural activation SCED (Gertler & Tate, 2019; Chapter 5) there was a range of specific challenges which are typical of this type of design. In particular there was the problem of measurement of an internal psychological state (mood) that is not necessarily observable by others. Depression is a difficult construct to measure because it largely relates to how a person subjectively “feels.” Measurement of the dependent variable in a SCED needs to be “precise, reliable and accurate so that they are free from bias” (Tate & Perdices, 2019). The dependent measure also needs to be replicable in order to prevent risk of bias due to inadequate sampling (Tate et al., 2013). The research program attempted to obviate this problem by measuring proxy behaviours associated with activity participation that were observable and objectively defined, and by applying a mood measure similar to the SIMS rather than a more traditional questionnaire. However, the mood measure still relied on participants themselves to collect the data because other people independent of the participant were not available to take on this role. This introduces another risk of bias in that the participants (as assessors) could not be blinded to the phase of the study and were also reporting the outcome measures. Ideally, target behaviours and outcome measures would be conducted by independent observers who were blind to the phase of the study (Tate et al., 2016; Tate et al., 2013).

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<sup>1</sup> Note: Nguyen et al. (2017) was not included for consideration in Chapter 2.2 Addendum to the Cochrane Review because it did not specify a diagnosis of depression or elevated depression symptoms in the inclusion criteria.



#### **6.4 Future directions of research**

As discussed earlier in this chapter, the past decade has seen greater interest in studies of non-pharmacological interventions for depression following TBI. Prior to 2009 there was only a single RCT of an intervention applicable to depression for people with TBI who were actually significantly depressed and a decade later there are 10 of which this author is aware. The Cochrane review (Gertler et al., 2015; Chapter 2, section 1) now reflects some, but not all, of the literature that is currently available. In the first instance it is important to undertake a substantial revision of the Cochrane review to identify all relevant RCTs on this topic. It is particularly important to identify any studies that include participants under the age of 18 because none have been identified so far. This will involve not only adding the four additional published studies already identified and described in section 2 of Chapter 2, but also launching a fresh search of databases, journals, conferences, study registries and grey literature since February 2015. The next step would be to combine these new studies into meta-analyses and conduct GRADE analyses with the previous studies.

The SIMS (Gertler & Tate, 2020; Chapter 4) and SCED (Gertler & Tate, 2019; Chapter 5) studies provide a model upon which to build for future evaluation of clinical cases. By utilising SIMS, clinicians and researchers now have a validated tool to determine response to treatment, while treatment is ongoing, rather than having to wait until post-treatment measures are administered. There is potential to expand on the SIMS by replicating the study using mobile internet-connected devices to make data collection more convenient. Similarly, it is possible to provide objective data on activity participation much more easily in 2019, compared to when the SCED study was initiated. Were this study to be repeated it

would incorporate mobile technologies to attain objective activity data (as proxy measures related to depression), by functions such as step counting and geo-marking, thereby relying less on participants' self-report.

Engagement in activity is important, however it is only one aspect of depression and there remains the problem of identifying other objective measures of depression that might capture progress of the condition as a whole. If a biological marker of depression could be identified, this could provide an objective outcome measure that is distinct from activity participation. A recent systematic review (Cristea, Karyotaki, Hollon, Cuijpers, & Gentili, 2019) found that biological markers of treatment response are rarely reported in trials of psychological interventions for depression, but the most common markers are glycaemic or immunological responses or cortisol levels. Other methods have included blood pressure recordings, neuroimaging (positron emission tomography or single-photon emission computed tomography), brain activity (electroencephalogram) or blood lipids. Of the meta-analyses conducted by Cristea et al. there was no clear effect of treatment on biological markers. The authors opined that this was either due to inconsistencies in measurement or that, in fact, psychological interventions did not lead to change in any biological marker. Alternatively, Lopez, Kos, and Turecki (2018) have identified that genetic markers (MicroRNAs) have potential to be measures of treatment response for patients with depression. If a biological marker could be identified that was applicable to depression post-TBI, a future study could incorporate this as an objective measure of treatment response.

Finally, the SCED study required substantial enquiry into data analytic techniques. When the study was initiated there was a dearth of literature, accessible to researchers in

neurorehabilitation, to inform how to analyse and interpret behavioural data. The methods that were applied in the SCED study would make an ideal template for the evaluation of a variety of treatments for emotional (and other cognitive and neurobehavioural) disorders in a neurological population and would warrant development of a data analytic program and accompanying manual.

## **6.5 Conclusions**

This thesis represents a comprehensive and integrated body of work investigating the treatment of depression following TBI. The program of research sprung from over a decade of the author's clinical practice treating people with depression following TBI. Despite Prigatano's (1991) call to action almost 30 years ago, there remained insufficient evidence to say that interventions for depression were applicable or effective for people with TBI-related impairments. It was within that context that the author sought validation for his own clinical practice and, in the process, answer a set of research questions. This occurred over a period of almost a decade in which there has been a substantial increase in interest in this topic. Researchers in this field might reflect upon the 2010s as being a turning point in tackling depression post-TBI not just because of the volume of research but also the consistency in evaluating interventions that has enabled comparisons to be drawn among studies.

There are various conclusions to be drawn from the research program. We found that CBT was the most evaluated intervention, but we did not find this to be effective unless it was

augmented with additional treatment over a longer period of time. During this time ACT has also become a part of neurorehabilitation and has promising initial findings.

Given the limited evidence available within currently published literature, this research program was able to show how interventions could be evaluated. This was by establishing a valid measure of mood (SIMS) as a convenient way for researchers and clinicians to track how clients/participants are responding to treatment. By using the SCED methodology in this research program, researchers can determine whether new treatment modes can be effective and can identify which components of treatment might be the most effective. This opens up a host of possibilities for future experimentation that could expand on existing interventions, incorporate new types of interventions and/or evaluate new modes of delivering interventions and outcome measures. This is important work considering the enduring effects of TBI across age groups, the large proportion of people with TBI who will continue to suffer from depression for years after their injuries, and the extent to which depression limits participation and quality of life.

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Pre/post-injury and therapy process factors. *Cognitive Therapy and Research*, 26(1),

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## **APPENDIX A**

### ***Author's publications and presentations***

**AUTHOR'S PUBLICATIONS AND PRESENTATIONS**

*(In reverse chronological order)*

**Publications**

**Gertler, P., & Tate, R. L.** (2020). Are single item mood scales (SIMS) valid for people with traumatic brain injury? *Brain Injury*. Advanced online publication. DOI: 10.1080/02699052.2020.1733087

**Gertler, P., & Tate, R. L.** (2019). Behavioural Activation Therapy to improve participation in adults with depression following brain injury: a single-case experimental design study. *Neuropsychological Rehabilitation*. doi: 10.1080/09602011.2019.1696212

McDonald, S., Trimmer, E., Newby, J., Grant, S., **Gertler, P.**, & Simpson G. K. (2019). Providing on-line support to families of people with brain injury and challenging behaviour: A feasibility study. *Neuropsychological Rehabilitation*, doi: 10.1080/09602011.2019.1696846

**Gertler, P., & Cameron, I.** (2018). Making sense of data analytic techniques used in a Cochrane systematic review. *Brain Impairment*, 19(1), 81-90. doi:10.1017/BrImp.2017.27

**Gertler, P., Tate, R. L., & Cameron, I. D.** (2015). Non-pharmacological interventions for depression in adults and children with traumatic brain injury. *Cochrane Database of Systematic Reviews* (12), CD009871. doi:10.1002/14651858.CD009871.pub2

McDonald, S., Tate, R., Togher, L., Bornhofen, C., Long, E., **Gertler, P.**, Bowen, R. (2008).

Social skills treatment for people with severe, chronic acquired brain injuries: a multicenter trial. *Archives of Physical Medicine and Rehabilitation*, 89,1648-59.

**Gertler, P.** (2006). Angry young men: aggressive behaviour after traumatic brain injury (cover feature). *InPsych*, October 2006, 22-23.

Hodgson, J., McDonald, S., Tate, R. and **Gertler, P.** (2005). A randomised controlled trial of a cognitive-behavioural therapy program for managing social anxiety after acquired brain injury. *Brain Impairment*, 6, 169-180.

Williamson, J.P., Illing, R., **Gertler, P.**, Braude, S. (2004). Near-drowning treated with therapeutic hypothermia. *Medical Journal of Australia*, 181, 500-501.

McGuire, B.E., **Gertler, P.**, Kowalczyk, A., Leeder, G. & Yeates, G. (2000). A paper and pencil version of the Rivermead Route and Messages sub-test. *Clinical Neuropsychological Assessment*, 1, 275-282.

## Conference presentations

**Gertler, P. & Tate, R.L. (2015).** *Behaviour activation therapy to improve participation and mood of people with depression following brain injury.* Neuropsychological Rehabilitation Special Interest Group of the WFNR, 12th NR-SIG-WFNR Conference. Daydream Island, Australia

**Gertler, P., Tate, R.L. and Cameron, I. (2015).** *Non-pharmacological interventions for depression in adults and children with traumatic brain injury: a systemic review.* 5<sup>th</sup> INS/ASSBI Pacific Rim Conference. Sydney, Australia.

**Gertler, P., Tate, R.L. & Cameron, I. (2011).** *A systematic review of non-pharmacological treatments for depression after TBI.* 8th conference of the Neuropsychological Rehabilitation Special Interest Group of the World Federation for NeuroRehabilitation. 11th – 12th July, 2011. Rotorua, NZ.

**Gertler, P., Tate, R.L. & Cameron, I. (2011).** *Treating depression following traumatic brain injury: are psychological treatments effective?* AACBT 34th National Conference. 26th – 30th October 2011. Sydney, Australia.

Lane-Brown, A., Simpson, G.K, **Gertler, P.** (presenting author) and Hodgkinson, A. (2013). A community-based participation-focused rehabilitation model of care after extremely severe traumatic brain injury. *Meeting of the Australasian Society for the Study of Brain Impairment, Hobart, Australia.*

**Gertler, P.** (2006). *Treating a client with TBI and health anxiety using a modified cognitive-behavioural approach*. 29<sup>th</sup> Annual Conference of the Australian Society for the Study of Brain Impairment: 27<sup>th</sup> – 29<sup>th</sup> April 2006. Rydges Jamison, Sydney.

**Gertler, P.** (2003). *Applying Behaviour Management Principles in a Community Outreach Program*. 26<sup>th</sup> Annual Conference of the Australian Society for the Study of Brain Impairment: 3<sup>rd</sup> – 5<sup>th</sup> April, 2003. Masonic Centre, Sydney

**Gertler, P., McGuire, B. and Kowalczyk, A.** (2000). *Reliability of the recovery locus of control scale following brain injury*. Poster presentation delivered at the Conference on Neuropsychological Rehabilitation. November 2000. Westminster, London.

## **APPENDIX B**

### ***Brain Impairment: Instructions for contributors***

## Brain Impairment

### Other actions

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Journal of the Australasian Society for the Study of Brain Impairment (ASSBI) (<http://www.assbi.com.au/>)

Published on behalf of The Australasian Society for the Study of Brain Impairment

## Instructions for contributors

### Brain Impairment

*These instructions follow the latest edition of the [Publication Manual of the American Psychological Association](http://www.apastyle.org/) (<http://www.apastyle.org/>). Authors of research manuscripts are strongly encouraged to follow relevant reporting guidelines as outlined in the special editorial: *Use of Reporting Guidelines in Scientific Writing: PRISMA, CONSORT, STROBE, STARD and Other Resources*, *Brain Impairment*, 12, 1–21 (<https://journals.cambridge.org/action/displayAbstract?fromPage=online&aid=849539%200&fulltextType=ED&fileId=S1443964600002217>). A statement confirming ethics approval should be included in all research manuscripts.*

### Aims and Scope

A multidisciplinary Journal of the Australasian Society for the Study of Brain Impairment (ASSBI).

The journal addresses topics related to the aetiology, epidemiology, treatment and outcomes of brain impairment with a particular focus on the implications for functional status, participation, rehabilitation and quality of life. Disciplines reflect a broad multidisciplinary scope and include neuroscience, neurology,



neuropsychology, psychiatry, clinical psychology, occupational therapy, physiotherapy, speech pathology, social work, and nursing. Submissions are welcome across the full range of conditions that affect brain function (stroke, tumour, progressive neurological illnesses, dementia, traumatic brain injury, epilepsy, etc.) throughout the lifespan.

## Manuscript Submissions

All manuscripts must be submitted to the Journal through the online submission system:  
<http://mc.manuscriptcentral.com/bim> (<http://mc.manuscriptcentral.com/bim>)

If you encounter any problems or have any queries about submitting your paper please contact the Editors-in-Chief:

**Jennifer Fleming** ([j.fleming@uq.edu.au](mailto:j.fleming@uq.edu.au) (<mailto:j.fleming@uq.edu.au>)) or **Grahame Simpson** ([Grahame.Simpson@sswahs.nsw.gov.au](mailto:Grahame.Simpson@sswahs.nsw.gov.au) (<mailto:Grahame.Simpson@sswahs.nsw.gov.au>))

All articles are refereed. Papers submitted to the journal must not have been published previously or submitted for publication to any other journal and must represent original work.

Note: Please note that the submission instructions have recently been updated with the addition of three required statements that must be included in all submissions. Please see the 'Required Statements' section below for further details.

## Article Categories

### Original articles

Articles in this category describe ethically approved research projects which generate new knowledge. A general guide for length is 5,000 words; however the length of manuscripts should be appropriate to the content and research approach.

### Review articles

Reviews of the literature which present a synthesis and critique of existing research using a formal method such as systematic review or scoping review format. Length is dependent upon the topic and scope of literature presented with up to 7,000 words recommended.

### Brief Report

Articles less than 3,000 words in length which present research findings that are less substantial than an original article, either in scope or content, for example, small pilot studies.

### **Clinical Practice: Current Opinion**

This category includes clinical case descriptions, clinical opinion pieces, or articles which present new directions in brain impairment research or service delivery, and should be less than 3,000 words.

### **Research Protocol**

Papers describing the background, rationale and methods of a proposed project, and similar in length and scope to original articles.

## **Manuscript Preparation**

Manuscripts must be presented double spaced in a clear, readable typeface (Times preferred), in an A4-size document with 3cm margins. Number all pages except the figures, beginning with the first page.

### **Title Page**

Your submission should have a separate title page bearing the name(s) and affiliation(s) of the contributing author(s). An email address and/or fax/telephone numbers are required for contact purposes and should be stated following the corresponding author's address in a footnote on the title page.

### **Headings**

Provide headings that subdivide the paper into its key areas. Reports of empirical studies will generally follow a sequence of headings, including method, results and discussion. Review, theoretical, case study and other papers need not follow such a format but should provide a logical structure and appropriate section headings.

### **Style**

The written paper should be logical, economical and precise in structure and use of language.

### **Tables**

Reserve tables for important data directly related to the content of the paper. A well-constructed table should enable data to be isolated from the text and presented in a way that enables the reader to quickly see patterns and relationships of the data not readily discernible in the text. Use brief but explanatory

table titles. The table title is placed at the top of the table. Include each table on a separate sheet. When constructing tables use tabs to space your columns as this will make it much easier to typeset the table in the text.

## Figures

Figures should be prepared to the correct size (max. width up to 120 mm) and each one supplied as an individual file, separate to the manuscript Word file. Include placement instructions in the Word document, such as 'Insert Figure 1 here'. The figure title is placed at the bottom of the figure. Prior to sending artwork, the separate files of figures, graphs, illustrations, should be printed by the author to test that the fonts have been embedded correctly and there is no distortion in the artwork as any such faults cannot be corrected by the publisher.

## Referencing

References and citations should follow the APA format. Some examples to assist you are provided below.

### Citations in text

**For a single author:** In a recent review, Smith (1992) suggested that ... A recent review (Smith, 1992) suggested that ... In 1992, Smith suggested that ...

**For two authors:** In a recent review, Smith and Watson (1992) suggested that ... A recent review (Smith & Watson, 1992) suggested that ... In 1992, Smith and Watson suggested that ...

**When a work has three, four, or five authors:** Cite all authors the first time the reference occurs; thereafter, the name of the first author followed by et al. (e.g., Smith et al., 1991).

The full list of authors must be cited in the list of references at the end of the paper. If use of the 'et al.' format gives rise to confusion, with another work of the same year and with the same first author, the references should be differentiated by the use of alphabet sequence following the publication year (e.g., Smith et al., 1991a; Smith et al., 1991b).

**When a work has six or more authors:** Cite only the surname of the first author, followed by et al.; in the reference list, provide initials and surnames of the first six authors followed by an ellipsis and the final author.

**General:** Within a paragraph the year need not be repeated in subsequent citations of the same study provided the study cannot be confused with other studies cited in the paper. When citing several studies within the same set of parentheses, the following format should be adhered to '... several studies (Brooks, 1974a, 1974b; Cairns et al., 1992; Miller, in press; Smith, 1992; Tarter et al., 1985, 1987; Watson & Smith, 1990) have reported that ...'.

## Reference List

**Chapter in an edited book:** Heilman, K.M., Watson, R.T., & Valenstein, E. (1985). Neglect and related disorders. In K.M. Heilman & E. Valenstein (Eds.), *Clinical neuropsychology* (2nd ed., pp. 243–293), New York: Oxford University Press.

**Complete book:** Lezak, M.D. (1983). *Neuropsychological assessment* (2nd ed.). New York: Oxford University Press.

**Paper published in a journal:** Tate, R.L., & Broe, G.A. (1999). Psychosocial adjustment after traumatic brain injury: what are the important variables? *Psychological Medicine*, 29(03), 713–725.  
doi:10.1017/S0033291799008466.

**Published psychological or other test:** Kertesz, A. (1982). Western Aphasia Battery. New York: Grune & Stratton.

**Unpublished paper presented at a conference:** Walsh, K.W. (1986, August). Bridging the gaps in clinical neuropsychology: The applied scientist model. Paper presented at the 21st Annual Conference of the Australian Psychological Society, James Cook University, Townsville, Queensland.

**Theses:** Author, (Year). *Title*. Type of thesis, Institution, Location of Institution.

**General:** Papers in the Reference List should be listed alphabetically by first author, and then by date. Single author entries precede multiple author entries beginning with the same surname. References with the same first author and different second or third authors are arranged alphabetically by the surname of the second author, and so on.

## Acknowledgements

In a section before the references section you may acknowledge individuals or organisations that provided advice and support (non-financial). Formal financial support and funding should be listed in the following 'Financial Support' section.

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## **APPENDIX C**

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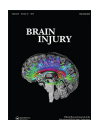
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3. You can opt to include a **video abstract** with your article. [Find out how these can help your work reach a wider audience, and what to think about when filming](#).
4. Between 3 and 5 **keywords**. Read [making your article more discoverable](#), including information on choosing a title and search engine optimization.
5. **Funding details.** Please supply all details required by your funding and grant-awarding bodies as follows:
  - For single agency grants*  
This work was supported by the [Funding Agency] under Grant [number xxxx].
  - For multiple agency grants*  
This work was supported by the [Funding Agency #1] under Grant [number xxxx];



[Funding Agency #2] under Grant [number xxxx]; and [Funding Agency #3] under Grant [number xxxx].

6. **Disclosure statement.** This is to acknowledge any financial interest or benefit that has arisen from the direct applications of your research. [Further guidance on what is a conflict of interest and how to disclose it.](#)
7. **Biographical note.** Please supply a short biographical note for each author. This could be adapted from your departmental website or academic networking profile and should be relatively brief (e.g., no more than 200 words).
8. **Data availability statement.** If there is a data set associated with the paper, please provide information about where the data supporting the results or analyses presented in the paper can be found. Where applicable, this should include the hyperlink, DOI or other persistent identifier associated with the data set(s). [Templates](#) are also available to support authors.
9. **Data deposition.** If you choose to share or make the data underlying the study open, please deposit your data in a [recognized data repository](#) prior to or at the time of submission. You will be asked to provide the DOI, pre-reserved DOI, or other persistent identifier for the data set.
10. **Supplemental online material.** Supplemental material can be a video, dataset, fileset, sound file or anything which supports (and is pertinent to) your paper. We publish supplemental material online via Figshare. Find out more about [supplemental material and how to submit it with your](#)

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Please include a disclosure statement, using the subheading "Disclosure of interest." If you have no interests to declare, please state this (suggested wording: *The authors report no conflict of interest*). For all NIH/Wellcome-funded papers, the grant number(s) must be included in the declaration of interest statement. [Read more on declaring conflicts of interest.](#)

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In order to be published in a Taylor & Francis journal, all clinical trials must have been registered in a public repository at the beginning of the research process (prior to patient enrolment). Trial registration numbers should be included in the abstract, with full details in the methods section. The registry should be publicly accessible (at no charge), open to all prospective registrants, and managed by a not-for-profit organization. For a list of registries that meet these requirements, please visit the [WHO International Clinical Trials Registry Platform \(ICTRP\)](#). The registration of all clinical trials facilitates the sharing of information among clinicians, researchers, and patients, enhances public confidence in research, and is in accordance with the [ICMJE guidelines](#).

### Complying With Ethics of

article.

11. **Figures.** Figures should be high quality (1200 dpi for line art, 600 dpi for grayscale and 300 dpi for color, at the correct size). Figures should be supplied in one of our preferred file formats: EPS, PDF, PS, JPEG, TIFF, or Microsoft Word (DOC or DOCX) files are acceptable for figures that have been drawn in Word. For information relating to other file types, please consult our [Submission of electronic artwork](#) document.
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### Consent

All authors are required to follow the [ICMJE requirements](#) on privacy and informed consent from patients and study participants. Please confirm that any patient, service user, or participant (or that person's parent or legal guardian) in any research, experiment, or clinical trial described in your paper has given written consent to the inclusion of material pertaining to themselves, that they acknowledge that they cannot be identified via the paper; and that you have fully anonymized them. Where someone is deceased, please ensure you have written consent from the family or estate. Authors may use this [Patient Consent Form](#), which should be completed, saved, and sent to the

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*Updated 18-01-2019*

## APPENDIX E

*University of Sydney: Guidelines for theses including publications*

Appendix D - University of Sydney: Guidelines for theses including publications

# Theses including publications

Under the [Thesis and examinations higher degrees by research policy 2015 \(pdf, 199KB\)](#), a research thesis is a coherent and cohesive narrative describing a body of scholarly activity that adds to knowledge.

At the University a collection of published papers is not a thesis, neither is a publication on its own sufficient to warrant the award of a research degree.

However, you can, and should, include papers you have published in your thesis. A thesis including publications (also called a thesis with publications) is one where the core chapters of your thesis consist of papers you have submitted for publication, have been accepted for publication, or have already been published. See our information on [preparing your thesis](#) for how to indicate that your thesis contains material you have published as part of your candidature.

A thesis including publication is suited to certain disciplines where your study progresses in discrete stages or involves a sequence of related components; for example, a series of lab experiments or several artworks.

One of the benefits of doing a thesis including publications is that you'll graduate with a number of publications to your credit. This will get your career as a researcher off to a good start.

You need to check with your faculty/school or department to see if a thesis including publications is possible and to find out their specific requirements. For more information see the [Thesis and examination of higher degrees by research policy 2015 \(pdf, 199KB\)](#).

The following is a general guide to some common requirements for a thesis including publications.

## Types of theses including publications

All chapters of your thesis can contain material previously published by you and need to be in a consistent format. Offprints are not considered chapters. These may be papers already published, submitted or accepted for publication, or not submitted.

Published papers need to be supplemented by an introduction (containing your aims and the context of the thesis) and a conclusion that synthesises the knowledge generated during your candidature. In some cases, thesis chapters are amended versions of published papers. The published papers are then put in the appendix.

## Papers

Only papers researched and written during your candidature can be included in your thesis. Some faculties or schools allow you to include papers regardless of their stage of publication. In other cases, papers need to have been accepted for publication, not just submitted and awaiting acceptance. You need to check with your faculty/school or department regarding their requirements.

## Journals

Papers need to be accepted by reputable, high-profile journals which require full peer review of contributions.

## Copyright

If you want your thesis to contain material you've published elsewhere, you need to get written permission from your publisher.

The University library has more [information on copyright](#).

## Authorship

You should be the main contributor and/or lead author to the papers you include. This means you have been responsible for the key ideas, the development of the study and the writing of the paper. It's possible to include papers co-written with other authors, as long as you have their permission (preferably in writing).

Find more [information about authorship attribution statements](#) and the format required.

## A cohesive thesis

The papers you submit need to form a cohesive whole. They need to be linked thematically, having a consistent focus on a particular topic. They also need a cohesive structure, including an introduction, explanatory material between the chapters and a conclusion.

The introduction and conclusion are particularly important in tying your thesis together. Coherence can be made explicit throughout your thesis. You could link your chapters using:

- the list of publications, where you can note which publication corresponds to which chapter
- a concept map or a flowchart at the end of the introduction
- the literature review, where you refer to how the chapters fill in particular gaps in the literature

- a page or half-page introduction or 'bridging section' before each chapter of the body, or at the end of each chapter
- the discussion section, referring back to the various papers.

You don't need all of these features, but the more links you can establish between the various parts of your thesis the more coherent it will be.

## List of publications

You need to include a list of publications either before or after the table of contents. In this section, you can link the publications to the specific chapter in which they are found. Many theses also record the bibliographical details of the article on the title page of each chapter.

If you need to include a co-author contribution statement, this is usually put with the list of publications or before each chapter.

Find more [information about authorship statements](#) and the format required.

## Literature reviews

There are different ways you can give context for your research when you do the literature review for each paper. For example:

- paraphrasing rather than repeating the same information
- where you integrate reviews in the main literature review in the introduction and cut down the literature reviews in the articles
- making each literature review substantially different
- removing the article(s)'s literature review, but only if the published chapter is presented in manuscript form.

## Discussion section

Your final discussion section draws together the main points from the discussion in each chapter into a single discussion. You need to avoid presenting or repeating in detail your ideas in the final discussion chapter by chapter or aim by aim, as this will not meet the requirements of a thesis. A way of doing this is to frame the discussion broadly, always in respect to 'this thesis/research project' or 'this thesis'.

## Reference lists

- When all articles are in journal format, their individual reference lists are included. This means the reference list at the end of the thesis contains only references from the introduction/literature review and discussion/conclusion.
- When all articles are in manuscript form, there is often no reference list attached to individual articles. Instead, all references are listed at the end of the thesis.
- Some theses have a separate reference list at the end of each chapter, including the introduction/conclusion.

## Page numbers

Most theses show both the thesis page number and the journal article page numbers. However, you could omit the thesis page number.

Source:

<https://sydney.edu.au/students/hdr-research-skills/theses-including-publications.html>



## **APPENDIX F**

***Ethics approval letters***

17 July 2012

Professor Robyn Tate  
Rehabilitation Studies Unit  
Sydney Medical School  
The University of Sydney  
[rtate@med.usyd.edu.au](mailto:rtate@med.usyd.edu.au)

Dear Professor Tate

Thank you for your correspondence dated 13 July 2012 addressing comments made to you by the Human Research Ethics Committee (HREC). I am pleased to inform you that with the matters now addressed your protocol entitled **“Evaluating psychological treatments for behavioural consequences after acquired brain injury”** has been approved.

Details of the approval are as follows:

**Protocol No.:** 14939  
**Approval Date:** 17 July 2012  
**First Annual Report Due:** 31 July 2013  
**Authorised Personnel:** Professor Robyn Tate  
Mr Paul Gertler  
Professor Ian Cameron

**Documents Approved:**

Document	Version Number	Date
Participant Information Statement	1	24/4/2012
Participant Consent Form	1	24/4/2012
Interview Guide	1	Submitted 15/5/2012
DASS21	1	Submitted 15/5/2012
Daily Monitoring Sheet	1	Submitted 15/5/2012

HREC approval is valid for four (4) years from the approval date stated in this letter and is granted pending the following conditions being met:

**Condition/s of Approval**

- Continuing compliance with the National Statement on Ethical Conduct in Research Involving Humans.

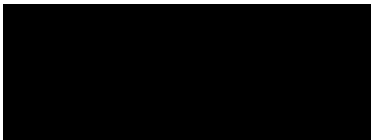
- Provision of an annual report on this research to the Human Research Ethics Committee from the approval date and at the completion of the study. Failure to submit reports will result in withdrawal of ethics approval for the project.
- All serious and unexpected adverse events should be reported to the HREC within 72 hours.
- All unforeseen events that might affect continued ethical acceptability of the project should be reported to the HREC as soon as possible.
- Any changes to the protocol including changes to research personnel must be approved by the HREC by submitting a Modification Form before the research project can proceed.

**Chief Investigator / Supervisor's responsibilities:**

1. You must retain copies of all signed Consent Forms and provide these to the HREC on request.
2. It is your responsibility to provide a copy of this letter to any internal/external granting agencies if requested.

Please do not hesitate to contact Research Integrity (Human Ethics) should you require further information or clarification.

Yours sincerely



**Dr Margaret Faedo**  
**Manager, Human Ethics**  
*On behalf of the HREC*

**cc: [paul@gertlerpsychology.com.au](mailto:paul@gertlerpsychology.com.au)**

**This HREC is constituted and operates in accordance with the National Health and Medical Research Council's (NHMRC) National Statement on Ethical Conduct in Human Research (2007), NHMRC and Universities Australia Australian Code for the Responsible Conduct of Research (2007) and the CPMP/ICH Note for Guidance on Good Clinical Practice.**

**Research Integrity & Ethics Administration**  
Human Research Ethics Committee

Wednesday, 4 October 2017

Prof Robyn Tate  
Northern Clinical School: Medicine; Sydney Medical School  
Email: robyn.tate@sydney.edu.au

Dear Robyn

The University of Sydney Human Research Ethics Committee (HREC) has considered your application.

After consideration of your response to the comments raised your project has been approved.

Approval is granted for a period of four years from **04 October 2017** to **04 October 2021**

**Project title:** Measuring mood after brain injury

**Project no.:** 2017/482

**First Annual Report due:** 04 October 2018

**Authorised Personnel:** Tate Robyn; Gertler Paul; Martens Rebecca;

**Documents Approved:**

Date Uploaded	Version number	Document Name
19/08/2017	Version 2	PIS for guardian/person responsible
19/08/2017	Version 1	New PIS in Easy English
19/08/2017	Version 1	New PCF in Easy English
19/08/2017	Version 1	PCF for guardian/person responsible - unchanged
19/08/2017	Version 2	WHODAS proxy form
20/05/2017	Version 1	DASS21 questionnaire
20/05/2017	Version 1	Satisfaction with life scale
20/05/2017	Version 1	Verbal mood scale and demographic questions
20/05/2017	Version 1	Visual mood scale
20/05/2017	Version 1	PIS General
20/05/2017	Version 1	PCF General

**Condition/s of Approval**

- Research must be conducted according to the approved proposal.
- An annual progress report must be submitted to the Ethics Office on or before the anniversary of approval and on completion of the project.
- You must report as soon as practicable anything that might warrant review of ethical approval of the project including:
  - Serious or unexpected adverse events (which should be reported within 72 hours).
  - Unforeseen events that might affect continued ethical acceptability of the project.

- Any changes to the proposal must be approved prior to their implementation (except where an amendment is undertaken to eliminate *immediate* risk to participants).
- Personnel working on this project must be sufficiently qualified by education, training and experience for their role, or adequately supervised. Changes to personnel must be reported and approved.
- Personnel must disclose any actual or potential conflicts of interest, including any financial or other interest or affiliation, as relevant to this project.
- Data and primary materials must be retained and stored in accordance with the relevant legislation and University guidelines.
- Ethics approval is dependent upon ongoing compliance of the research with the *National Statement on Ethical Conduct in Human Research*, the *Australian Code for the Responsible Conduct of Research*, applicable legal requirements, and with University policies, procedures and governance requirements.
- The Ethics Office may conduct audits on approved projects.
- The Chief Investigator has ultimate responsibility for the conduct of the research and is responsible for ensuring all others involved will conduct the research in accordance with the above.

This letter constitutes ethical approval only.

Please contact the Ethics Office should you require further information or clarification.

Sincerely



**Professor Glen Davis**  
Chair  
Human Research Ethics Committee (HREC 2)

**The University of Sydney HRECs are constituted and operate in accordance with the National Health and Medical Research Council's (NHMRC) National Statement on Ethical Conduct in Human Research (2007) and the NHMRC's Australian Code for the Responsible Conduct of Research (2007).**