The associations of psychological distress and pain with cognitive functioning

in hospitalized individuals following mild traumatic brain injury.

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Abstract

The influence of psychological distress and pain on cognitive outcome following mild traumatic brain injury (mTBI) has received little empirical attention. The current research explored the associations of psychological distress and pain with cognitive functioning in adults following mTBI. A systematic review (Study 1) and two empirical studies (Studies 2 and 3) were undertaken. A systematic review was conducted to identify and evaluate the existing evidence regarding the relationship between psychological distress and cognitive functioning following mTBI. The search yielded 17 relevant papers. Evaluation of the design and methodology of the studies revealed that the quality of the evidence was limited. A prospective longitudinal study of consecutive trauma patients suggested lower cognitive performance in the presence of depressive symptoms. In an empirical investigation, 57 consecutive mTBI patients admitted to a Level 1 trauma hospital were recruited. Within 14 days of injury, participants completed self-report measures of acute post-traumatic stress, depression, and pain, and neuropsychological measures of attention, memory, processing speed, reaction time, working memory, and verbal fluency. In Study 2, canonical correlation analyses explored whether acute post-traumatic stress, depression, and pain were related to cognitive performance in a number of domains. Acute post-traumatic stress and pain were significantly associated with speed and accuracy performance on an extended version of the Ruff 2 & 7 Selective Attention Test. Study 3 further analyzed performance on this task using repeated measures multivariate analyses of variance. Performance was tested under three conditions of increasing cognitive demand (standard, auditory distraction, and dual-task conditions). Acute post-traumatic stress was associated with lower accuracy while depression was associated with higher accuracy. Acute post-traumatic stress, depression, and pain were associated with differential changes in speed performance as cognitive demands increased. The results highlight the potential for complex associations of acute post-traumatic stress, depression, and pain with cognitive functioning in the acute to sub-acute phase of mTBI.

Accurate differential diagnosis in neuropsychological assessment and rehabilitation efforts

may benefit from understanding the nature of these relationships.

Statement of Candidate

I certify that the work in this thesis entitled *The associations of psychological distress and pain with cognitive functioning in hospitalized individuals following mild traumatic brain injury* has not previously been submitted for a degree nor has it been submitted as part of requirements for a degree to any other university or institution other than Macquarie University.

I also certify that the thesis is an original piece of research and it has been written by me. Any help and assistance that I have received in my research work and the preparation of the thesis itself have been appropriately acknowledged.

In addition, I certify that all information sources and literature used are indicated in the thesis.

The research presented in this thesis was approved by Macquarie University Ethics Review Committee, reference number 5201100172, on 24th of February, 2011.

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Outline

The aim of the current research was to investigate the associations of psychological distress and pain with cognitive functioning following mild traumatic brain injury (mTBI). Chapter 1 provides a description of mTBI that includes diagnostic classification, epidemiology, and pathophysiology. Cognitive, emotional, and pain outcomes are outlined with a focus on the acute to sub-acute recovery period (up to 30 days post-injury; McCrea et al., 2009). This chapter concludes with an introduction to the aims and hypotheses of the current research.

Chapter 2 presents a systematic review of the existing evidence (Study 1). This systematic review focuses on the relationship between psychological distress and cognitive functioning following mTBI in adults. Acute to sub-acute (up to 30 days post-injury) and post-acute (greater than 30 days post-injury; McCrea et al., 2009) outcomes are addressed.

Chapter 3 presents an empirical investigation using a consecutive sample of adult trauma patients with mTBI (Study 2). Canonical correlation analyses were used to explore whether self-report measures of psychological distress and pain were associated with cognitive performance on a neuropsychological battery in the acute to sub-acute phase following mTBI. The analyses examined relationships between i) acute post-traumatic stress, depression, and pain, and ii) cognitive performance on neuropsychological measures of attention, memory, processing speed, reaction time, working memory, and verbal fluency.

Chapter 4 presents further analysis of the same empirical data (Study 3). Repeated measures multivariate analyses of variance further evaluated whether acute post-traumatic stress, depression, and pain were related to speed and accuracy performance on an attentional task, namely an extended version (Cicerone, 1996) of the Ruff 2 & 7 Selective Attention Test (Ruff & Allen, 1996). The task was completed under three conditions of increasing cognitive demands: standard, auditory distraction, and dual-task conditions (Cicerone, 1996). Cognitive performance under these three conditions was analyzed to determine whether associations

with acute post-traumatic stress, depression, and pain differed as cognitive demands increased.

Chapter 5 summarizes the main conclusions of the aforementioned studies. The strengths and limitations of the research are considered. Implications for clinical practice and future research are also discussed.

While every attempt has been made to reduce replication of material across the chapters of this thesis, due to the nature of a thesis by publication, similarities may exist between chapters.

Chapter 1

Introduction

Introduction

Definition of Mild Traumatic Brain Injury

Mild traumatic brain injury (mTBI) is defined as an acute brain injury which is the result of mechanical energy imparted by external forces (Carroll, Cassidy, Holm, Kraus, & Coronado, 2004). The classification of mTBI (Carroll, Cassidy, Holm, et al., 2004) is operationally defined by

- at least one of the following (i) confusion or disorientation, (ii) a loss of consciousness (LOC) no longer than 30 minutes, (iii) post-traumatic amnesia (PTA) for less than 24 hours, or (iv) transient neurological abnormalities such as focal neurological signs, seizures, and intracranial lesions not requiring surgery;

- a Glasgow Coma Scale (GCS) score of 13–15 after 30 minutes post-injury or later upon presentation for healthcare.

These indicators of mTBI cannot be due to drugs, alcohol, or medications, and cannot be caused by penetrating craniocerebral injury, other injuries, treatment, or other problems (such as language fluency or co-existing medical conditions; Carroll, Cassidy, Holm, et al., 2004, p.115). A mTBI may be further classified as a *complicated* mTBI (D. H. Williams, Levin, & Eisenberg, 1990) when an intracranial abnormality is identified on day-of-injury neuroimaging (Iverson et al., 2012) and all other criteria for mTBI are met. Patients with complicated mTBIs have shown worse neuropsychological and emotional outcomes compared to patients with uncomplicated mTBIs (Borgaro, Prigitano, Kwasnica, & Rexer, 2003; Iverson, 2006; Kurča, Sivák, & Kučera, 2006; Lange, Iverson, & Franzen, 2009; D. H. Williams et al., 1990; but see also Iverson et al., 2012; Sadowski-Cron et al., 2006). For this reason, some authors have suggested that complicated mTBIs should be subsumed under a distinct severity category (Kashluba, Hanks, Casey, & Millis, 2008; D. H. Williams et al., 1990).

Epidemiology

MTBI has been recognized as a major public health problem (Finch, Clapperton, & McCrory, 2013; Hyder, Wunderlich, Puvanachandra, Gururaj, & Kobusingye, 2007; National Institutes of Health (NIH) Consensus Development Panel on Rehabilitation of Persons With Traumatic Brain Injury, 1999). The Centers for Disease Control and Prevention (Faul, Xu, Wald, & Coronado, 2010) recently estimated that 1.7 million civilians in the United States of America (USA) sustain a TBI every year. Many estimates of incidence rates are based on data collected from emergency department (ED) visits or hospital admissions. Consequently, these estimates do not include the substantial proportion of people who sustain mTBI and do not seek medical attention, or who seek medical attention within primary care or outpatient settings (Feigin et al., 2013; Sosin, Sniezek, & Thurman, 1996).

After reviewing the epidemiological literature on mTBI, Cassidy et al. (2004) suggested that the true rate of all mTBI likely exceeds 600 per 100,000 person-years. A recent population-based study in New Zealand substantiated this proposition and revealed the widespread extent of mTBI incidence (Feigin et al., 2013). By reviewing information from multiple overlapping sources, including public and private hospitals, health centers, family physicians, and community services, Feigin et al. documented every new case of TBI, treated or untreated, in a specified geographical area that was demographically representative of the entire New Zealand population. The authors reported the overall incidence of all-severity TBI was 790 per 100,000 person-years. Ninety-five percent of the TBIs were mild (equating to a mTBI incidence of 749 per 100,000 person-years). A recent study in the US that randomly sampled population-based data collected between 1985 and 1999 also suggested a preponderance of mTBI (accounting for approximately 92% of all suspected TBIs; Leibson et al., 2011).

Males and young adults are consistently found to be at higher risk of sustaining a mTBI (Cassidy et al., 2004; Feigin et al., 2013; Leibson et al., 2011; Sosin et al., 1996).

Minority ethnic groups may also be at increased risk of this type of injury (Feigin et al., 2013). The most common mechanisms of injury include fall, motor vehicle accident, and assault (Cassidy et al., 2004; Feigin et al., 2013; Helps, Henley, & Harrison, 2008). Sports-related injury has also been noted to contribute to a substantial proportion of mTBI (Finch et al., 2013; Sosin et al., 1996). Another mechanism of mTBI not addressed by the abovementioned literature, is military service, for which high rates of mTBI have been recorded (Hoge et al., 2008).

TBI has been estimated to comprise 15.1% of all hospitalizations in the US (Faul et al., 2010). Direct health care costs incurred due to mTBI hospitalizations have been valued at $16.7 billion in the USA annually (Thurman, 2001). In Australia, the estimated annual cost of acute hospitalization due to TBI was $184 million (Helps et al., 2008). Another Australian study (Finch et al., 2013) also indicated substantial direct health care costs due to hospitalized sports-related mTBIs; the authors calculated an annual cost of $1.99 million incurred by one Australian state. Because a sizeable proportion of mTBI cases are not admitted to hospital (Feigin et al., 2013; Sosin et al., 1996), these figures likely underestimate the true economic burden (Borg et al., 2004; Langlois, Rutland-Brown, & Wald, 2006; McCrea, 2008; Thurman, 2001), particularly when indirect costs, such as lost productivity, are also taken into account (Borg et al., 2004).

Pathophysiology

The pathophysiology of TBI is predominantly characterized by traumatic axonal injury (Iverson, Lange, Gaetz, & Zasler, 2006). The mechanical force to the head distorts brain tissue and stretches axons beyond typical tolerance limits (Bigler & Maxwell, 2012a). In milder forms of TBI, immediate shearing of axons is not common (Iverson et al., 2006). The stretching of axons nevertheless initiates a complex cascade of pathophysiological changes (Giza & Hovda, 2001). Several reviews have outlined these mechanisms (Bigler & Maxwell, 2012b; Iverson, 2005; Iverson et al., 2006). Initially, axonal stretching induces

ionic shifts in and out of the cell, including a dramatic influx of calcium. This calcium influx affects both the structural and functional integrity of the cell. Structurally, calcium destroys microtubules, which are thick fibers that help to support the axonal cytoskeleton. Calcium influx also causes axonal swelling, which can eventually lead to separation but not necessarily death of the cell (Iverson, 2005). Functionally, calcium influx forms part of a larger cascade that causes metabolic dysfunction, which can eventually lead to energy failure. Because neurons rely on axonal integrity and metabolic homeostasis, these processes impair neural functioning.

In milder injuries, these pathophysiological processes are transient and generally normalize over time (Bigler & Maxwell, 2012b; Iverson et al., 2006). This time course varies with the severity of the injury, with more severe injuries requiring a longer period for cellular functioning to return to baseline levels. In mild injuries, neurophysiological recovery is believed to occur over the days and weeks following injury (Bigler & Maxwell, 2012b).

Ommaya and Gennarelli (1974) proposed a model to describe the areas of the brain that are most affected by traumatic forces. They proposed that, during a mechanical impact, brain tissue is strained in a centripetal sequence. According to this sequence, mild acceleration–deceleration forces primarily disturb the surface structures of the cortex and associated white matter. As forces become more severe, deeper parts of the brain are progressively affected. This model has garnered empirical support (Gaetz, 2004). Due to differences in the type and location of impacts causing mTBIs, the sites of greatest tissue injury vary widely between patients (Bigler & Maxwell, 2012b). In the regions affected by mTBI, small numbers of damaged axons appear to cluster in discrete areas amongst other unaffected neurons (Iverson, 2005). Overall, these reviews indicate that mTBI involves minimal and temporary disruption to a relatively small number of neurons (Iverson et al., 2006), which results in transient deficits in functional connectivity and neuropsychological processes (Bigler & Maxwell, 2012a).

Acute to Sub-Acute Cognitive Outcomes (up to 30 days post-injury)

The acute and sub-acute recovery periods following mTBI have been defined as up to 5 days post-injury, and between 5 to 30 days post-injury, respectively (McCrea et al., 2009). In a comprehensive, systematic, and critical review of the mTBI literature, Carroll, Cassidy, Peloso, and colleagues (2004) reported that there was "consistent and methodologically sound evidence of cognitive deficits within the first few days after the injury, including problems of recall of material, speed of information processing and attention" (p. 88). Meta-analytic reviews have confirmed a significant effect of mTBI on cognition within the first 3 months post-injury (Belanger, Curtiss, Demery, Lebowitz, & Vanderploeg, 2005; Frencham, Fox, & Maybery, 2005; Rohling et al., 2011; Schretlen & Shapiro, 2003). The greatest impairment has been observed proximal to the injury, followed by cognitive recovery, a large proportion of which occurs across the first 30 days post-injury (Belanger et al., 2005; Frencham et al., 2005; Rohling et al., 2011; Schretlen & Shapiro, 2003). Effects on global cognitive indices have been reported as small to medium in size during the first month post-injury ($d = -0.29$ to -0.41; Rohling et al., 2011; Schretlen & Shapiro, 2003). The domains of memory, attention, working memory, processing speed, executive functioning, fluency, and language skills are impacted across the first 3 months (Belanger et al., 2005; Frencham et al., 2005; Rohling et al., 2011). Memory, attention, processing speed, and verbal skills have shown the most pronounced reductions, that were, on average, medium in effect size (Belanger et al., 2005; Frencham et al., 2005; Rohling et al., 2011). Recent prospective trauma studies that have compared mTBI patients to injured controls have added to the evidence of cognitive deficits in the acute to sub-acute phase (Landre, Poppe, Davis, Schmaus, & Hobbs; 2006; Levin et al., 2013; Peterson, Stull, Collins, & Wang, 2009; Ponsford et al., 2000; Ponsford, Cameron, Fitzgerald, Grant, & Mikocka-Walus, 2011; Sheedy, Geffen, Donnelly, & Faux, 2006). Mild TBI patients in these studies showed lower performance relative to injured controls on measures of memory, reaction time, visuomotor speed, and processing speed across the first

week post-injury (Landre et al., 2006; Levin et al., 2013; Peterson et al., 2009; Ponsford et al., 2000; 2011; Sheedy et al., 2006).

Although this literature reflects a pattern of transient cognitive deficits followed by full recovery in most trauma patients with mTBI, significant heterogeneity has been reported amongst results (e.g., Belanger et al., 2005; Peterson et al., 2009; Ponsford et al., 2011). Some researchers have raised concerns about the potential weaknesses of a meta-analytic approach (Iverson, 2010; Pertab, James, & Bigler, 2009). These authors emphasize that aggregate analyses may obscure individual differences in performance and limit statistical precision by combining neuropsychological tests that reflect multifarious abilities, or which have differential sensitivity. Thus, individual outcomes may vary, and some mTBI patients may have poorer long-term cognitive or psychological outcomes (e.g., Ponsford et al., 2000; Ruff et al., 1994). Such poor outcomes may be due to factors other than the mTBI itself (Dikmen & Levin, 1993; Iverson, 2010). For example, the neuropsychological performance of mTBI patients may be affected by pre-existing factors (e.g., learning disability; Dicker, 1992), comorbid clinical conditions (e.g., depression; Ghaffar, McCullagh, Ouchterlony, & Feinstein, 2006), social psychological influences (e.g., diagnosis threat; Suhr & Gunstad, 2002), or motivational factors (e.g., test effort; Curtis, Thompson, Greve, & Bianchini, 2008).

Acute to Sub-Acute Psychological Outcomes (up to 30 days post-injury)

One factor that may affect mTBI patients' performance on neuropsychological measures is psychological distress. Psychological outcomes have received comparatively less attention following mTBI. In a meta-analytic investigation, Panayiotou, Jackson, and Crowe (2010) identified 11 studies that compared mTBI participants with controls on measures of emotional functioning. Effect sizes that were weighted by sample size indicated small significant effects of mTBI on reporting of depression and anxiety, however, estimates obtained using inverse variance weighting methods were not significantly different from zero (Panayiotou et al., 2010). The analysis was limited by the small number of included studies

which mostly assessed patients in the post-acute recovery period (beyond 30 days post-injury; McCrea et al., 2009), precluding firm conclusions about the prevalence of psychological difficulties experienced after mTBI in the acute to sub-acute period. Additionally, as mentioned previously, meta-analysis may not capture subgroups of individuals who experience significant distress (Iverson, 2010).

Prospective studies of consecutive trauma patients have provided more detailed information regarding psychological outcomes. These studies have indicated that symptoms of post-traumatic stress (Broomhall et al., 2009; Levin et al., 2013) and depression (Federoff et al., 1992) are frequently reported by mTBI patients across the first month post-injury. Broomhall and colleagues (2009) found that while 4.62% of mTBI patients met full criteria for acute stress disorder (ASD), including dissociative, re-experiencing, avoidance, and arousal symptom clusters, (*Diagnostic and Statistical Manual of Mental Disorders* [*DSM*], 4th ed.; American Psychiatric Association [APA], 1994), a further 19.12% met criteria for subsyndromal ASD (defined as patients meeting criteria for at least one ASD symptom cluster). Federoff and colleagues (1992) reported that, at around one month post-injury, 23% of mTBI patients (defined as a GCS score between 12 and 15) met criteria for major depression (*DSM*, 3rd ed.; APA, 1980). Other studies that have used case–control or non-consecutive samples from trauma settings also indicate a high rate of psychological symptoms in mTBI patients, including anxiety (Meares et al., 2006), acute post-traumatic stress (Harvey & Bryant, 1998), and depression (Harvey & Bryant, 1998; Meares et al., 2006). High comorbidity has also been noted between acute post-traumatic stress and depression during this period (Harvey & Bryant, 1998). Finally, mTBI patients may be particularly vulnerable to acute psychological distress when compared to traumatically non-brain injured control groups (Bazarian et al., 1999; Broomhall et al., 2009; Levin et al., 2013), however, this vulnerability has not always been replicated (Ponsford et al., 2011). It is worthwhile to note that very few researchers have utilized diagnostic interviews in the measurement of

psychological distress. Instead, many have used self-report questionnaires of psychological symptoms which may overlap with other sequelae of mTBI (e.g. 'postconcussive symptoms'; Iverson, 2006; Iverson & McCracken, 1997). Factors that may be associated with increased risk of psychological ill health following mTBI include female sex, previous psychiatric disorder, current substance abuse, current pain, involvement in litigation, and fewer years of education (Deb, Lyons, Koutzoukis, Ali, & McCarthy, 1999; Fann et al., 2004; Feinstein, Hershkop, Jardine, & Ouchterlony, 2000; Levin et al., 2001). Comorbid physical injury does not appear to be associated with higher risk of psychological distress (Fann et al., 2004).

Acute to Sub-Acute Pain Outcomes (up to 30 days post-injury)

Pain is an important aspect of outcome following mTBI (Faux, Sheedy, Delaney, & Riopelle, 2011; Jamora, Schroeder, & Ruff, 2013; Landre et al., 2006; Meares et al., 2008; 2011). Prospective studies of consecutive trauma admissions have indicated that pain is a common complaint amongst mTBI patients in the acute to sub-acute phase (Alves, Macciocchi, & Barth, 1993; Faux et al., 2011; Landre et al., 2006; Ponsford et al., 2011). As a part of a cross-validation study examining mTBI outcomes, Faux and colleagues (2011) found that headache was reported by 77% of participants assessed within EDs in Australia and Canada. Similarly, Ponsford and colleagues (2011) reported that 78.9% of mTBI participants complained of headaches within 48 hours of injury. Pain may be related to psychological functioning following mTBI (Jamora et al., 2013), although this has been observed only in the post-acute injury phase in a sample of referred patients. Literature on the topic of post-traumatic headache suggests elevated rates of pain among females and those experiencing psychological distress (Lew et al., 2006). Compared to patients who suffer more severe TBIs, those who sustain mTBI appear to be at greater risk of chronic pain syndromes (Nampiaparampil, 2008).

A Gap in the Literature

Cognitive deficits, psychological symptoms, and pain are commonly experienced during the acute to sub-acute phase following mTBI. Despite the prevalence of psychological complaints and pain amongst mTBI patients, few studies have examined their impact on cognitive outcome (Carroll, Cassidy, Peloso, et al., 2004; Jamora et al., 2013; E. L. Moore, Terryberry-Spohr, & Hope, 2006). Longstanding calls to address these issues (Alexander, 1995; Carroll, Cassidy, Peloso, et al., 2004; Dikmen & Levin, 1993; E. L. Moore et al., 2006) appear to have remained largely unanswered.

The impact of psychological distress on cognitive performance. Meta-analytic research in the field of psychiatry has demonstrated cognitive impairment in individuals with anxiety disorders, such as post-traumatic stress disorder (PTSD; Castaneda, Tuulio-Henriksson, Marttunen, Suvisaari, & Lönnqvist, 2008; Johnsen & Asbjørnsen, 2008), panic disorder (Castaneda et al., 2008), and obsessive–compulsive disorder (Castaneda et al., 2008; Henry, 2006), and in those with major depressive disorder (Castaneda et al., 2008; Lee, Hermens, Porter, & Redoblado-Hodge, 2012). Deficits in attention (Lee et al., 2012), processing speed (Lee et al., 2012), memory (Castaneda et al., 2008; Johnson & Asbjørnsen, 2008; Lee et al., 2012), fluency (Henry, 2006), and executive functions (Castaneda et al., 2008; Henry, 2006; Lee et al., 2012) have been reported.

Investigations using non-clinical samples have similarly demonstrated detrimental effects of subclinical symptoms and induced mood states on cognitive functioning (Darke, 1988; Derakshan & Eysenck, 2009; Eysenck, Derakshan, Santos, & Calvo, 2007; Pacheco-Unguetti, Acosta, Callejas, & Lupiáñez, 2010; Salthouse, 2012; Seibert & Ellis, 1991). Negative impacts have been noted on attentional skills (Pacheco-Unguetti et al., 2010), working memory (Darke, 1988; Derakshan & Eysenck, 2009; Eysenck et al., 2007), memory (Seibert & Ellis, 1991), executive functions (Derakshan & Eysenck, 2009; Eysenck et al., 2007) and general measures of cognitive ability (Salthouse, 2012).

It is unknown whether psychological distress experienced in the acute to sub-acute period following mTBI similarly influences cognitive functioning. The current research aims to examine the association between psychological distress and cognitive functioning in the acute to sub-acute phase following mTBI.

The impact of pain on cognitive performance. The experience of pain is closely associated with psychological distress. Affective qualities are integral to definitions and conceptualizations of pain (Gatchel, Peng, Peters, Fuchs, & Turk, 2007; Merskey & Bogduk, 1994; Price, 2000). Empirically, pain is strongly associated with psychopathology in both clinical (Dickens, McGowan, Clark-Carter, & Creed, 2002; Fishbain, 2013; Linton, 2000) and population-based samples (Gerhardt et al., 2011; L. J. Williams, Pasco, Jacka, Dodd, & Berk, 2012). Pain and distress may also mutually maintain each other (Asmundson, Coons, Taylor, & Katz, 2002; Dersh, Polatin, & Gatchel, 2002; Sharp & Harvey, 2001). For example, pain and post-traumatic stress may mutually maintain each other through common attentional and cognitive biases, such as heightened expectation and overestimation of the probability of threatening or painful stimuli (Asmundson et al., 2002; Sharp & Harvey, 2001). Misinterpretation of physical symptoms, avoidant coping styles, and pain acting as a persistent reminder of the trauma may also contribute to mutual maintenance (Asmundson et al., 2002; Sharp & Harvey, 2001).

A number of reviews report that pain may negatively affect neuropsychological performance (Hart, Martelli, & Zasler, 2000; Moriarty, McGuire, & Finn, 2011; Nicholson, 2000). Most of this research has been conducted using chronic pain samples or via the experimental induction of acute pain in healthy individuals. The chronic pain literature generally indicates a detrimental effect on cognition in a number of chronic pain conditions (e.g., chronic musculoskeletal pain, arthritis, and fibromyalgia; Hart et al., 2000; Moriarty et al., 2011; Nicholson, 2000). Reductions have been observed in processing speed, attention, working memory, memory, psychomotor skills, and in performance on more complex tasks,

however, there is variability among results (Hart et al., 2000; Moriarty et al., 2011; Nicholson, 2000). Neuropsychological investigations in chronic pain samples have been fraught with methodological weaknesses, including small samples, lack of control groups, reliance on retrospective methods, and limited assessment of the nature or severity of pain (Hart et al., 2000; Nicholson, 2000). Additionally, individuals with chronic pain frequently present with issues that may confound neuropsychological assessment, such as comorbid psychological disorders, fatigue and sleep disturbances, use of opioid analgesia, as well as involvement in litigation or compensation (Hart et al., 2000; Moriarty et al., 2011; Nicholson, 2000). Suboptimal effort may also be a factor that contributes to the neuropsychological performance of chronic pain patients (Etherton, Bianchini, Ciota, Heinly, & Greve, 2006; Etherton, Bianchini, Heinly, & Greve, 2006) although one study has found processing speed deficits in chronic pain patients despite evidence of sufficient effort on formal measures (Etherton, Bianchini, Heinly, & Greve, 2006). Temporal factors, such as the chronicity of pain, may also moderate the relationship between pain and cognition (Moriarty et al., 2011). Additionally, the pathophysiology of chronic pain may differ qualitatively from that of acute pain (Cervero & Laird, 1996).

Relatively few studies have used experimentally induced acute pain (D. J. Moore, Keogh, & Eccleston, 2009) and those results are variable. Some investigations have found higher scores on cognitive tasks in the presence of pain (e.g., Babiloni et al., 2004; Seminowicz & Davis, 2007); others have indicated lower scores (e.g., Etherton, Bianchini, Heinly, & Greve, 2006; Sanchez, 2011). Some studies have indicated higher and lower scores depending on the task (e.g., Patil, Apfelbaum, & Zacny, 1995), whereas others have found no significant impact of acute pain on cognitive performance (e.g., Etherton, Bianchini, Ciota, Heinly, & Greve, 2006; Velhuijzen, Kenemans, de Bruin, Olivier, & Volkerts, 2006). Aside from their heterogeneity, the application of these results to mTBI patients is also problematic because experimentally induced pain is typically less distressing and shorter in duration than

real-world acute pain (Edens & Gil, 1995; Gagliese, 2007; Patil et al., 1995). Additionally, many of these studies have used experimental cognitive paradigms (D. J. Moore et al., 2009), such as the go/no–go task (Babiloni et al., 2004), which may not necessarily translate to effects on standard neuropsychological tasks.

A recent review highlighted the potential for alternative methods to model and study naturalistic pain (D. J. Moore, Keogh, Crombez, & Eccleston, 2013). One recent study investigated naturally occurring pain among university students and staff who were identified as tension-type headache sufferers (D. J. Moore, Keogh, & Eccleston, 2013). Individuals were tested in the presence and absence of headache using various attentional paradigms. The authors (D. J. Moore, Keogh, & Eccleston, 2013) reported that headache was associated with lower performance on selected measures of response speed and accuracy, however, they did not assess the influence of additional symptoms (such as nausea and sensitivity to light or sound) or psychological distress.

Despite their methodological shortcomings, the abovementioned studies underscore the potential for pain to modulate cognitive functioning following mTBI. In addition to examining the association between psychological distress and cognitive functioning, the current research aims to evaluate the association between pain and cognitive functioning in the acute to sub-acute recovery period following mTBI.

Theoretical considerations. Several researchers have suggested that psychological distress and pain consume cognitive resources (Andrews & Thomson, 2009; Beck, 1985; Eccleston & Crombez, 1999; Ellis & Ashbrook, 1988; Eysenck et al., 2007; Grigsby, Rosenberg, & Busenbark, 1995; Legrain et al., 2009; Pessoa, 2009; Sanchez, 2011). Such resources typically refer to attentional (Ellis & Ashbrook, 1988) or working memory stores or capacity (Eysenck et al., 2007; Sanchez, 2011). Because these cognitive resources are assumed to be limited in their capacity (Baddeley, 2003; Kahneman, 1973; Moray, 1967; Norman & Bobrow, 1975), the consumption of resources by psychological distress (Ellis &

Ashbrook, 1988; Eysenck et al., 2007; Seibert & Ellis, 1991) and pain (Eccleston & Crombez, 1999; Legrain et al., 2009; Sanchez, 2011) can lead to difficulties in cognitive performance.

The *attentional control theory* (Eysenck et al., 2007) proposes that anxiety causes attentional resources to be allocated to threat-related stimuli, thereby reducing attentional focus on the current task. Eysenck et al. specify that anxiety impairs aspects of the central executive component of working memory (Baddeley, 2003) which are involved in attentional control. These aspects include the abilities of *inhibition* and *shifting*, which are respectively required to resist disruption or interference, and shift between tasks (Derakshan & Eysenck, 2009; Eysenck et al., 2007; Friedman & Miyake, 2004; Miyake, Friedman, Emerson, Witzki, & Howerter, 2000). The anxious individual is consequently more susceptible to distraction and has greater difficulty moving from one attentional focus to another (Eysenck et al., 2007). In this way, anxiety strengthens the influence of *bottom-up processes* of attentional capture whereby sensory input automatically proceeds to be perceived and then acted upon without feedback or control from "higher" cortical centers (see Corbetta & Shulman, 2002; Miller & Cohen, 2001). In the anxious individual, these bottom-up processes prevail over goal-directed *top-down processes* of attentional control whereby neural signals originating from prefrontal areas influence "lower" neural centers to guide attention according to the individual's motivations and intentions (Corbetta & Shulman, 2002; Miller & Cohen, 2001). Anxious individuals attempt to compensate for this inefficiency by increasing their effort or recruiting auxiliary processing resources. This compensation consequently reduces *task efficiency* (often measured through time taken to complete the task) to a greater extent than *task effectiveness* (measured via task accuracy; Eysenck et al., 2007). There is considerable empirical support for this theory (Derakshan & Eysenck, 2009; Eysenck et al., 2007; Eysenck, Payne, & Derakshan, 2005).

In the *resource allocation model,* Ellis and Ashbrook (1988) similarly propose that depression consumes cognitive resources because depression causes an individual to think

about their mood state. The authors (Ellis & Ashbrook, 1988) suggest that task-irrelevant thoughts about mood reduce the individual's ability to allocate processing resources to other tasks, such as encoding of new memories, leading to reduced recall. This theory has received some empirical support (Ellis & Ashbrook, 1988), and has been further elaborated by Andrews and Thomson (2009). The latter noted that deficits ostensibly caused by task-irrelevant processing may be obviated or reversed by interventions that encourage depressed individuals to disengage from task-irrelevant thoughts and focus on the current task (Hertel & Rude, 1991; Lyubomirsky, Kasri, & Zehm, 2003).

Similar proposals have been described in the context of pain (Eccleston & Crombez, 1999; Legrain et al., 2009; Sanchez, 2011). Eccleston and Crombez (1999) argue that pain acts as a warning to the organism or individual regarding potential threat. Pain demands and captures attention in order to prompt the selection of an appropriate response or course of action to promote survival (Eccleston & Crombez, 1999). Legrain et al. (2009) extended this theory to a neurocognitive model which suggests that pain captures attention via bottom-up processes to influence behaviour without intentional control from higher prefrontal cortical areas (see Corbetta & Shulman, 2002; Miller & Cohen, 2001). While there is some evidence for attentional capture by pain, particularly in chronic pain patients (Crombez, Van Ryckeghem, Eccleston, & Van Damme, 2013), evidence regarding the effect of acute non-induced pain on cognitive performance remains preliminary (D. J. Moore, Keogh, & Eccleston, 2013). Data regarding the neurocognitive model of pain is in an early stage of development (Legrain et al., 2009).

These theories propose that anxiety, depression, and pain may consume cognitive resources otherwise required for cognitive task performance. Such conceptualizations may be useful when considering how psychological distress and pain might affect cognitive performance following mTBI. Overall, these theories suggest that anxiety, depression, and pain following mTBI may be associated with lower performance on cognitive tasks.

The pathophysiology of mTBI may also be regarded as a temporary reduction of neural resources. Metabolic dysfunction and compromised structural integrity involved in traumatic axonal injury leads to impaired neural functioning and connectivity which normalizes over time (Bigler & Maxwell, 2012b; Iverson, 2005). If a mTBI limits neural resources, patients may be particularly susceptible to further reductions in neural resources such as those associated with the experiences of psychological distress and pain. This may be especially so during the acute to sub-acute period when mTBI pathophysiological processes are at their peak.

The Role of Increased Cognitive Demands

MTBI studies. When investigating whether psychological distress and pain may modulate cognitive performance following mTBI, it is important to utilize tests that provide sensitivity to detect potentially subtle differences in outcome (Bernstein, 1999; Gronwall, 1991; Mateer & Mapou, 1996). Tests that involve increased levels of *cognitive demand* may confer the greatest sensitivity (Bernstein, 1999; Mateer & Mapou, 1996). The effect of increased cognitive demand on mTBI patients' performance has been tested by manipulating task characteristics, such as increasing difficulty or complexity (Bernstein, 2002; Cudmore, Segalowitz, & Dywan, 2000; Tombaugh, Rees, Stormer, Harrison, & Smith, 2007), increasing the quantity of stimuli to be processed (McAllister et al., 2001; Pardini et al., 2010), or extending task duration (Cicerone, 1996). The number of tasks to be performed simultaneously may also be increased, such as in dual-task paradigms (Bernstein, 2002; Blanchet, Paradis-Giroux, Pépin, & McKerral, 2009; Cicerone, 1996; Cudmore et al., 2000; De Monte et al., 2005; Paré, Rabin, Fogel, & Pépin, 2009; Segalowitz, Bernstein, & Lawson, 2001). Finally, cognitive demand may be manipulated environmentally by including distractors (Cicerone, 1996), or by placing physiological stress on the individual (Ewing, McCarthy, Gronwall, & Wrightson, 1980).

The results of these studies have suggested that tasks involving greater cognitive demands, or tasks completed under more demanding conditions, may be more sensitive to the cognitive effects of mTBI than standard neuropsychological tasks (Bernstein, 2002; O'Jile et al., 2006; Stuss et al., 1985). They have additionally indicated that, compared to control groups, mTBI patients may show greater declines in performance as demands increase within a specific cognitive task (Blanchet et al., 2009; Cicerone, 1996; Paré et al., 2009; Segalowitz et al., 2001). Although others have not found greater performance decrements among mTBI patients with increasing cognitive demand (Cudmore et al., 2000; De Monte et al., 2005; McAllister et al., 1999; 2001), the tasks used in these latter studies may not have been sufficiently sensitive to detect subtle changes in performance or demanding enough to elicit differences between mTBI participants and controls.

Studies have indicated lower performance on more demanding cognitive measures in mTBI participants up to 6.4 years post-injury despite performance within normal limits on standard neuropsychological tasks (Cicerone, 1996; Segalowitz et al., 2001; Stuss et al., 1985). Studies conducted within the acute to sub-acute phase have not found any significant difference between tasks of differing cognitive demand (De Monte et al., 2005; McAllister et al., 1999; 2001), however, differential change in performance with increasing demand has been observed in mTBI patients within a week of injury (Paré et al., 2009). It is unclear whether these discrepancies in results are attributable to differences in sample size, task sensitivity, or other methodological differences between studies. It is also possible that more severe cognitive impairment in the acute to sub-acute phase of mTBI may overwhelm subtle differences that occur in response to varying demands.

Methodological features of the abovementioned studies indicate that the current evidence regarding increased demands and task sensitivity following mTBI is limited in quality. Many of these studies recruited small non-consecutive samples of referred patients (Cicerone, 1996; Stuss et al., 1985) or university students (Bernstein, 2002; Segalowitz et al.,

2001). Such samples may not be representative of the broader population of people who sustain mTBI (Belanger et al., 2005; Dikmen & Levin, 1993). Additionally, small samples (McAllister et al., 1999; 2001; Segalowitz et al., 2001) may not confer sufficient statistical power to detect differences on less demanding or standard neuropsychological tasks. One methodologically strong study, which recruited a large group of consecutive mTBI participants from an ED, found that speed performance of mTBI participants tested within a week of injury was more vulnerable to increased demands when compared to healthy controls (Paré et al., 2009). Although these results require replication with a trauma control group (Larrabee, Binder, Rohling, & Ploetz, 2013), they suggest that tasks with increasing levels of cognitive demand may be particularly sensitive in detecting subtle differences between the cognitive performance of mTBI patients and appropriate control groups in the acute to sub-acute phase.

Theoretical considerations. The abovementioned theories regarding the impact of psychological distress and pain on cognition (e.g., Ellis & Ashbrook, 1988; Eysenck et al., 2007; Sanchez, 2011) provide specific predictions regarding increased cognitive demands. As discussed, these theories assume that cognitive resources are limited in capacity (Baddeley, 2003; Kahneman, 1973; Moray, 1967; Norman & Bobrow, 1975), and that distress and pain consume cognitive resources. As distress and pain increase and consume more cognitive resources, less auxiliary cognitive resources are available to cope with greater task demands (Ellis & Ashbrook, 1988; Eysenck et al., 2007; Sanchez, 2011). Consequently, psychological distress and pain are predicted to have greater impacts on cognitive performance as the demand for cognitive resources increases (Ellis & Ashbrook, 1988; Eysenck et al., 2007; Sanchez, 2011).

Summary of the role of increased cognitive demands. Cognitive tasks which incorporate increased levels of demand, or which are completed under particularly demanding conditions, may be particularly sensitive to differences in outcome following mTBI.

Theoretical proposals also suggest that the level of cognitive demand may moderate the impact of psychological distress and pain on cognitive performance.

Aims and Hypotheses of the Current Research

The primary aim of the current research was to examine whether psychological distress and pain are associated with cognitive functioning following mTBI.

Study 1.

Aim. To systematically review the existing evidence regarding the relationship between psychological distress and cognitive functioning following mTBI in adults.

Study 2.

Aim. To explore whether psychological distress—specifically, acute post-traumatic stress and depression—and pain are associated with cognitive performance on measures of attention, memory, processing speed, reaction time, working memory, and verbal fluency in adult trauma patients within 14 days of mTBI.

Hypothesis. It was hypothesized that acute post-traumatic stress, depression, and pain would be associated with lower cognitive performance on neuropsychological measures.

Study 3.

Aims. (1) To further evaluate whether acute post-traumatic stress, depression, and pain are associated with cognitive performance on the extended version of the Ruff 2 & 7 Selective Attention Test in adult trauma patients within 14 days of mTBI, (2) to examine whether the associations of psychological distress and pain to performance on the extended Ruff 2 & 7 task differ as cognitive demands increase, (3) to evaluate whether acute post-traumatic stress, depression, and pain are associated with subjective ratings of mental effort expended during completion of the extended Ruff 2 & 7, and (4) to assess whether self-reported psychiatric history and recent opioid intake (during the 24 hours prior to assessment) are related to the associations of psychological distress and pain with cognitive performance.

Hypotheses. It was anticipated that (1) acute post-traumatic stress, depression, and pain would be associated with lower scores on speed and accuracy measures of the extended Ruff 2 & 7 task, (2) acute post-traumatic stress, depression, and pain would be associated with larger declines in speed and accuracy scores as cognitive demands increased, (3) acute post-traumatic stress, depression, and pain would be associated with higher subjective ratings of mental effort, and (4) self-reported psychiatric history may be related to the association between psychological distress and cognitive performance while recent opioid intake may be related to the association between pain and cognitive performance.

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Chapter 2

The relationship between psychological distress and cognitive outcome following mild

traumatic brain injury: A systematic review

Abstract

The effect of psychological distress on cognitive outcome following mild traumatic brain injury (mTBI) has been a focus of interest in recent years. To summarize current knowledge of this topic, a systematic review was conducted of the evidence regarding the relationship between psychological distress and cognitive functioning in adult mTBI patients. Searches of electronic databases PsycINFO, MEDLINE, PubMed, ScienceDirect, Scopus, Web of Science, EMBASE, CINAHL, and the Cochrane Library covering the period from January 1995 to October 2013 yielded 1759 unique references. Seventeen articles met the inclusion criteria. The evidence was found to be limited by a lack of representative samples and settings, and the use of weak study designs. Only one study prospectively recruited a consecutive trauma cohort. Incomplete reporting of the study design and methodology was common, as was the recruitment of small samples. Fifteen studies did not include an appropriate traumatically non-brain injured control group. Results suggest that depressive symptoms may be associated with lower cognitive performance on measures of attention, reaction time, and non-verbal abstract reasoning following mTBI. The evidence remains limited regarding associations between cognition and other forms of psychological distress (anxiety and post-traumatic stress). Future research is required to confirm and further explore the relationship between psychological distress and cognitive outcome following mTBI.

The Relationship between Psychological Distress and Cognitive Outcome following Mild

Traumatic Brain Injury: A Systematic Review

Mild traumatic brain injury (mTBI) is a highly prevalent (Cassidy et al., 2004; Feigin et al., 2013) injury to the brain resulting from mechanical energy imparted by external forces (Carroll, Cassidy, Holm, Kraus, & Coronado, 2004). Cognitive sequelae of mTBI typically consist of mild reductions in attention, processing speed, memory, and executive functions (Belanger, Curtiss, Demery, Lebowitz, & Vanderploeg, 2005; Carroll, Cassidy, Peloso, et al., 2004; Frencham, Fox, & Maybery, 2005). These deficits are evident on neuropsychological testing (Belanger et al., 2005; Carroll, Cassidy, Peloso, et al., 2004; Frencham et al., 2005) and generally resolve within one to three months post-injury (Belanger et al., 2005; Binder, Rohling, & Larrabee, 1997; Frencham et al., 2005; Schretlen & Shapiro, 2003).

Symptoms of psychological distress including depression, anxiety, and traumatic stress, are also frequently reported (Bazarian et al., 1999; Broomhall et al., 2009; Meares et al., 2008; 2011) within the acute to sub-acute recovery phase following mTBI (defined as the post-injury periods up to 5 days, and between 5 to 30 days, respectively; McCrea et al., 2009). These symptoms can also present months after the injury (Bryant et al., 2010; Levin et al., 2005). Distress is frequently reported at clinically significant levels (Bryant et al., 2009; 2010; Deb, Lyons, Koutzoukis, Ali, & McCarthy, 1999; Fann et al., 2004) and comorbidity between different psychological disorders can be high (Bryant et al., 2010; Harvey & Bryant, 1998). Some evidence suggests that mTBI may impose additional vulnerability to psychological ill health beyond that of non-brain physical injury, particularly with respect to anxiety disorders (Bazarian et al., 1999; Broomhall et al., 2009; Bryant et al., 2009; 2010; Fann et al., 2004; Jorge et al., 2004; Levin et al., 2013). However, not all studies have indicated such a vulnerability (Meares et al., 2011; Ponsford, Cameron, Fitzgerald, Grant, & Mikocka–Walus, 2011).

Literature from the field of psychiatry suggests that forms of psychological distress, such as depression, anxiety, and traumatic stress, are associated with deficits in cognition (Castaneda, Tuulio–Henriksson, Marttunen, Suvisaari, & Lönnqvist, 2008; Johnsen & Asbjørnsen, 2008; Kuelz, Hohagen, & Voderholzer, 2004; Lee, Hermens, Porter, & Redoblado–Hodge, 2012). The influence of psychological distress on cognitive outcome following mTBI, however, has received little attention in the literature despite calls over many years for research to address this issue (Alexander, 1995; Carroll, Cassidy, Holm, et al., 2004; Dikmen & Levin, 1993; Moore, Terryberry–Spohr, & Hope, 2006). A search of the literature revealed there were no existing reviews on this topic. The aim of the current research was to systematically review the evidence regarding the relationship between psychological distress and cognitive outcome following mTBI in adults and to critically evaluate the quality of this literature.

Method

Search Strategy

A keyword-based search of the computerized databases PsycINFO, MEDLINE, PubMed, ScienceDirect, Scopus, Web of Science, EMBASE, CINAHL, and the Cochrane Library was conducted covering the period from 1 January 1995 to 13 October 2013 to identify articles that examined the relationship between psychological distress and cognitive functioning following mTBI. The search terms *distress*, *stress*, *anxi**, *depressi**, *mood*, *emotional*, *psychological*, *psychiatric*, *neuropsychiatric*, *post-traumatic stress*, *posttraumatic stress* were combined with *cogniti**, *neuropsycholog**, and *neurocogniti** and injury search terms *mild traumatic brain injury*, *minor traumatic brain injury*, *mild head injury*, *mild brain injury*, *minor head injury*, *minor brain injury*, *closed head injury*, *mild head trauma*, *minor head trauma*, *mTBI* and *concuss** (asterisks indicate the wildcard notation used in databases to indicate any combination of letters). In accordance with a priori inclusion criteria, limits

applied included human subjects, articles written in English, articles published in peer-reviewed journals, and adult group populations.

Results were compiled into an electronic reference database (Endnote, Version 4.0.2) and duplicates were removed. Titles and abstracts of remaining results were screened by the first author (JM) according to the inclusion and exclusion criteria. If it could not be determined from the title and abstract whether the study met these criteria, the full text was obtained and the method was read to determine eligibility. Reference lists from eligible articles were screened and experts in the field were consulted to identify any other potentially relevant articles not identified in the search. Potentially relevant articles identified from these additional searches underwent the same screening process.

Inclusion and Exclusion Criteria

Included studies met the following criteria: (1) used an adult sample; (2) employed at least one of the criterion commonly used for diagnosis of mTBI, namely, a Glasgow Coma Scale (GCS) score of 13–14 (American Congress of Rehabilitation Medicine [ACRM], 1993; Carroll, Cassidy, Holm, et al., 2004; Teasdale, 1995), a duration of post-traumatic amnesia (PTA) of less than 24 hours (ACRM, 1993; Carroll, Cassidy, Holm, et al., 2004; Teasdale, 1995) or a loss of consciousness (LOC) of less than 30 minutes (ACRM, 1993; Carroll, Cassidy, Holm, et al., 2004); (3) analyzed the relationship between the results of at least one standardized valid measure of current psychological distress and at least one standardized valid measure of neuropsychological function following mTBI (Anthony & Barlow, 2010; Strauss, Sherman, & Spreen, 2006); (4) peer-reviewed original empirical article written in English; and (5) published between 1 January 1995 and 13 October 2013. Studies with combined mild and moderate TBI samples were included as definitions of these severity classifications vary and overlap in some parameters (ACRM, 1993; Carroll, Cassidy, Holm, et al., 2004; Rimel, Giordani, Barth, Boll, & Jane, 1981; Rimel, Giordani, Barth, & Jane, 1982; Teasdale, 1995). Mixed mild to moderate TBI samples were included only if the majority of

participants (i.e., more than 50%) were classified as having sustained a mTBI. Studies were excluded if (1) mTBIs were combined with severe TBIs or other conditions and were not analyzed separately because the effects within mTBI could not be concluded from the results; (2) patients were sampled whose injuries were sustained in a military context due to the unique characteristics of this setting, including mechanisms of injury (e.g., blast exposure), the traumatic context of the injury, the presence of ongoing combat-related stressors, and challenges in timely and accurate diagnosis (Brenner, Vanderploeg, & Terrio, 2009; French, 2010; Iverson, Langlois, McCrea, & Kelly, 2009; Meares et al., 2011; Rigg & Mooney, 2011); or (3) they were case studies, case series, or non-empirical articles (e.g., reviews, editorials).

Study Design Evaluation

Study design was considered according to the hierarchy of evidence outlined by the National Health and Medical Research Council (NHMRC; 2009). This system ranks study designs according to the strength they confer in addressing research questions. Prospective cohort studies are ranked as the highest level of empirical evidence, surpassed only by a systematic review of prospective cohort studies. Retrospective cohort studies, case–control studies, cross-sectional studies, and case series are considered weaker levels of evidence.

Methodological Quality Evaluation

A critical appraisal tool with evidence of inter-rater reliability and content validity (Heacock, Koehoorn, & Tan, 1997) was used to assess the methodological quality of each article. When an item's rating was ambiguous, the second author (SM) was consulted and a decision was made by consensus. The total score comprised the sum of all critical appraisal items according to Heacock et al.'s scoring criteria. Because a number of critical appraisal items also refer to aspects of study design, the total score reflected a combination of both methodological and design quality ratings. Possible scores range from 0 to 12. According to Heacock et al., articles scoring more than 9 are considered *strong* academic papers, scores of

more than 6 and up to 9 are considered *moderately strong* and those scoring 6 or less are considered *weak*. Items include (1) Does the study identify a gap in the existing literature?; (2) Is the research question clearly stated?; (3) After reading the methodology section, could the reader repeat the study with confidence?; (4) Do the authors state the measurement technique(s)/instrument(s) are valid/reliable, or do they provide information so the reader can investigate the validity and reliability of the measurement technique(s)/instrument(s)?; (5) Is the study population representative of the end-user population? (a consecutive series of mTBI patients identified at the time of injury was considered to best represent the *end-user population*); (6) Is the study setting representative of the workplace to which the results will be applied? (the term *workplace* was understood to be a Level 1 trauma hospital or emergency department [ED] setting; Belanger et al., 2005; Dikmen & Levin, 1993); (7) Is there an appropriate control/comparison group? (an appropriate control or comparison group was understood to be a consecutive series of traumatically non-brain injured patients identified at the time of injury; Carroll, Cassidy, Peloso, et al., 2004; Dikmen & Levin, 1993; Larrabee, Binder, Rohling, & Ploetz, 2013); (8) Is there a statement about the sample size or power of the study?; (9) Do the authors state the statistical test used and the level of significance or confidence levels achieved?; (10) Do the authors discuss the limitations or biases of the study design and/or methodology?; (11) Do the authors discuss the effect of the preceding limitations or biases on the results?; (12) Do the authors achieve any one of the following: Utilize a study population $N \geq 30$; Conduct non-parametric statistics tests for $N < 30$; Conduct parametric tests for $N < 30$ but explain sample is normally distributed; or, Conduct multivariate tests with 10 times as many subjects as there are independent variables?; (13) Do the authors discuss recommendations of the findings for workers? (the term *workers* was understood to be a hospitalized mTBI population); and, (14) Do the authors identify opportunities for further research based on the current study? (p. 169; see Appendix A).

Data Extraction

A data extraction form was used to collect the following information: authors, date of publication, a brief description of how the sample was formed, study design, measures of psychological distress, cognitive tests demonstrating significant and non-significant associations with distress, and a summary of the relevant findings (see Table 1). Injury and demographic information was collected (see Table 2). This data included sample size, setting, mTBI classification, time between injury and assessment, age of the mTBI group and the gender of the sample. Due to the associations amongst litigation, suboptimal effort, and impaired neuropsychological performance following mTBI (Belanger et al., 2005; Stulemeijer, Andriessen, Brauer, Vos, & van der Werf, 2007), it was also noted whether participants were reported to be involved in litigation and whether measures of effort were used.

Results

The search yielded 4460 references in total, of which 1759 were unique (see Figure 1). Following the exclusion of 1506 records, 253 full text articles were screened. Seventeen studies met the inclusion criteria.

Study Design

Two studies were prospective longitudinal studies (Durazzo et al., 2013; Ghaffar, McCullagh, Ouchterlony, & Feinstein, 2006). Of these two, only Ghaffar et al. (2006) reported that they sampled from consecutive admissions. One other study was longitudinal but used a case–control design and did not specify whether participants were recruited prospectively or retrospectively (Rao et al., 2010). Another used a case–control design with participants drawn from consecutive mTBI presentations to an ED (Preece & Geffen, 2007). The remaining 13 studies were cross-sectional.

Table 1

Key Findings of Studies

Recovery Period	Setting	First Author, Year	Distress measures	Sig cognitive measures	NS cognitive measures	Findings	Quality rating
Acute–Sub-acute							
	ED	Preece, 2007	DASS-21 Dep; self-reported clinical depn diagnosis	HVLT-R d'	WAIS-R DSS; SCOLP; HVLT-R learning, delay recall	Depn related to worse verbal recognition in mTBI but not Ctl group.	strong
	Trauma hospital	Batchelor, 1995	STAI	Stroop	nil	State anx related to performance on attentional/ inhibition task.	mod
Post-acute							
	Trauma EDs	Ghaffar, 2006	GHQ-28 Dep	Stroop; SDMT; SRT; CRT; WAIS-III MR	PVSAT; WAIS-III VO, LNS; HVLT-R	Depn related to worse attention, reaction time, and non-verbal abstract reasoning.	strong
	ED	Durazzo, 2013	BDI; STAI	nil	CVLT-II; BVMT-R; TMT; WAIS-III SI, DSy, DSp, SS, BD, AR; Short Categories Test; Stroop; WCST-C; Luria-Nebraska Item 99; AMNART	Depn and anx not related to mean performance in any cognitive domain at either time point. Depn and anx also unrelated to change in performance from time 1 to time 2.	strong
	Neuro-surgical unit	Clarke, 2012	HADS; NEO-FFI: N	SDMT; TMT; WAIS-III WMI; RAVLT; RCF; COWAT	nil	Higher distress composite correlated with worse cognitive composite in mTBI. No association in Ctl groups.	strong

Table 1 *(Continued)*

Recovery Period	Setting	First Author, Year	Distress measures	Sig cognitive measures	NS cognitive measures	Findings	Quality rating
Post-acute							
	Neuro-trauma unit, OP rehab program	Beaupré, 2012	BDI-II; BAI	nil	TEA: Map Search, Telephone Search; Ruff 2 & 7 Selective Attention Test	No correlation between depn or anx and cognitive performance in mTBI group.	mod
	Trauma unit, BIU	Rao, 2010	SCID-IV Axis 1 disorders	nil	BTA; HVLT-R; BVMT-R; TMT; VF; Stroop; MMSE	No difference between dep and non-dep groups on cognitive measures.	mod
	Various	Hickling, 1998	CAPS	nil	RAVLT; TMT; Stroop; PASAT; hand tapping	In LOC group, no relationship between PTSD and cognition.	mod
	TBI clinic	Chamelian, 2006	SCID mood disorder section	WAIS-III WMI; BVMT-R immediate	CVLT-II; PASAT; WCST; BVMT-R delay	Major depn related to worse working memory and immediate visual recall.	mod
	TBI clinic	Rapoport, 2005	SCID depn module	WAIS-III WMI, PSI; WMS-III LM; CVLT; WCST persev	WCST categories; BVMT-R	Major depn related to worse working memory, processing speed, verbal memory, and perseveration.	mod
	Rehab center	Schnabel, 2012	BDI-II	nil	WMS-IV LM; WAIS-IV DSp	No correlation between depn and change in performance from standard to distraction condition in mTBI group.	mod

Table 1 *(Continued)*

Recovery Period	Setting	First Author, Year	Distress measures	Sig cognitive measures	NS cognitive measures	Findings	Quality rating
Post-acute							
	Conc-ussion clinic	Heitger, 2009	BDI-II	nil	WAIS-III DSy, DSp, SI, PC; WMS-III LM; RAVLT; RCF; TMT; ZM; VF; CWIT; WTAR	No association between depn and cognition.	mod
	Private practice	Sherman, 2000	MMPI-2 DEP	WAIS-R DSy; TMT	RCF; WAIS-R VO, CO, SI, BD, OA, DSp; BNT; WMS-R LM; WCST; PASAT; VF; Stroop	Depn related to worse visual attention/processing speed in mTBI.	mod
	Private practice	Ruttan, 2003	MCMI-II Dysthymia; MMPI-2 D, DEP, H–L scales	WMS-R LM	WMS-R VR; Category Test; TMT B; CCC	Sample 1: Depn predicted verbal recall; Sample 2: Depn by gender interactions predicted verbal recall when NRIs removed.	strong
	NR	Evered, 2003	MCMI-II or -III	SDNB attention/concentration, memory, motor, verbal, spatial, planning skills; WAIS-III IQ	SDNB learning, perception	Psychopathology related to worse attention/concentration, memory, motor, verbal, spatial, and planning abilities, and IQ.	mod
	NR	Raskin, 1998	MMPI clinical scales	nil	WAIS-R; RCF; WMS-R; TMT; SDMT; APT; VSA; WCST; CVLT; Stroop; WRAT-R2 AR; COWAT	No correlation between psychopathology and cognition. No difference between dep and non-dep.	mod

Table 1 *(Continued)*

Recovery Period	Setting	First Author, Year	Distress measures	Sig cognitive measures	NS cognitive measures	Findings	Quality rating
Post-acute							
	University	Suhr, 2005	BDI-II; STAI state version	nil	WAIS-III DSp, LNS, AR, DSy; TMT; RCF; WCST	No relationship between depn or anx and cognitive performance.	mod

Note. AMNART = American National Adult Reading Test; anx = anxiety; APT = Attention Process Test; AR = Arithmetic; BAI = Beck Anxiety Inventory; BD = Block Design; BDI = Beck Depression Inventory; BIU = brain injury unit; BNT = Boston Naming Test; BTA = Brief Test of Attention; BVMT = Brief Visuospatial Memory Test; CAPS = Clinician-Administered PTSD Scale; CCC = Consonant Trigrams Test; CO = Comprehension; COWAT = Controlled Oral Word Association Test; CRT = Choice Reaction Time; Ctl = control; CVLT = California Verbal Learning Test; CWIT = Colour Word Interference Test; D = depression clinical scale; DASS-21 Dep = Depression Anxiety Stress Scale 21-Item depression subscale; dep = depressed; depn = depression; DEP = depression content scale; DSp = Digit Span; DSS = Digit Symbol Substitution; DSy = Digit Symbol; d' = d prime recognition measure; ED = emergency department; GHQ-28 Dep = General Health Questionnaire 28-Item depression subscale; HADS = Hospital Anxiety and Depression Scale; H–L = Harris-Lingoes; HVLT = Hopkins Verbal Learning Test; LM = Logical Memory; LNS = Letter-Number Sequencing; LOC = loss of consciousness; MCMI = Millon Clinical Multiaxial Inventory; MMPI = Minnesota Multiphasic Personality Inventory; MMSE = Mini Mental State Examination; mod = moderately strong; MR = Matrix Reasoning; mTBI = mild traumatic brain injury; NEO-FFI:N = Neuroticism-Extroversion-Openness - Five Factor Inventory: neuroticism scale; NR = not reported; NRI = neurologically-relevant item; NS = non-significant; OA = Object Assembly; OP = outpatient; PASAT = Paced Auditory Serial Addition Test; PC = Picture Completion; persev = perseverative responses; PSI = Processing Speed Index; PTSD = post-traumatic stress disorder; PVSAT = Paced Visual Serial Addition Task; RAVLT = Rey Auditory Verbal Learning Test; RCF = Rey Complex Figure; rehab = rehabilitation; SCID = Structured Clinical Interview for DSM Disorders; SCOLP = Speed of Comprehension Test; SDMT = Symbol Digit Modalities Test; SDNB = San Diego Neuropsychological Test Battery; SI = Similarities; Sig = significant; SRT = Simple Reaction Time; SS = Symbol Search; STAI = State Trait Anxiety Inventory; TBI = traumatic brain injury; TEA = Test of Everyday Attention; TMT = Trail Making Test; VF = verbal fluency; VO = Vocabulary; VR = Visual Reproduction; VSA = Visual Speed and Accuracy; WAIS = Wechsler Adult Intelligence Scale; WCST = Wisconsin Card Sorting Test; WMI = Working Memory Index; WMS = Wechsler Memory Scale; WRAT-R2 = Wide Range Achievement Test – Revised Level 2; WTAR = Wechsler Test of Adult Reading; ZM = Zoo Map Test; -C = computer version; -R = revised; -II = 2nd ed.; -III = 3rd ed.; -IV = 4th ed.; -2 = 2nd ed.

Table 2

Sample, Setting, Injury, and Demographic Data

Recovery Period	First Author, Year	Sample and Setting	TBI definitions	Time post-injury (*SD*)	Mean TBI age (*SD*)	Sex (male%)
Acute–Sub-acute						
	Preece, 2007	30 mTBIs and 19 OI and UI Cs with depn; 30 mTBIs and 30 OI and UI Cs without depn from initial pool of 389 recruited from ED and advertisements.	Medical diagnosis, GCS 13–15, clear CT	9.4 (3.8) hr dep mTBI; 9.2 (3.3) hr non-dep mTBI; 13.5 (7.5) hr dep Cs; 10.9 (6.6) hr non-dep Cs	27.7 (9.1) dep; 24.6 (9) non-dep	80 mTBI; 33 Cs
	Batchelor, 1995	35 hospitalized MVA mTBIs from initial pool of 50; 35 HCs.	GCS 13–15, PTA < 48 hr	6.4 days (range 2–11 days)	25.6 (8.8)	63
Post-acute						
	Ghaffar, 2006	122 from 191 consecutive mTBI ED admits to two tertiary trauma centers.	ACRM	6 months	30.7 (10.9) treated; 33.3 (12.4) untreated	65
	Durazzo, 2013	25 non-smoking and 19 smoking mTBI ED admits; 20 HCs.	LOC < 30 min, GCS 13–15, PTA < 24 hr, no depressed skull fracture	38 (22) days; 230 (36) days	34.6 (12.1) nsm; 35.7 (10.9) sm; 40.2 (9.4) HC	76 nsm; 72 sm; 74 HC.
	Clarke, 2012	21 mTBI and 19 spinal patients without mTBI admitted to neurosurgical unit; 20 HC students.	GCS 13–15, LOC < 30 min, PTA < 24 hr, normal neuroimaging	between 3–12 months	35.6 (NR) (range 19–60)	67 mTBI; 74 spinal; 60 HC
	Beaupré, 2012	30 mTBIs recruited from neurotrauma unit and OP rehab program; 17 HCs.	ACRM	2.2 (0.5) months early; 5.6 (1.2) months late	39 (13) early; 38 (13) late	67 early; 87 late; 59 HC

Table 2 *(Continued)*

Recovery Period	First Author, Year	Sample and Setting	TBI definitions	Time post-injury (*SD*)	Mean TBI age (*SD*)	Sex (male%)
Post-acute						
	Rao, 2010	43 mTBIs recruited from trauma unit and brain injury unit	GCS < 15, LOC < 30 min	2 weeks (no cognitive measures), 2–3, 6, 12 months	44.5 (17.5)	53, (25 dep; 60 non-dep)
	Hickling, 1998	107 MVA survivors, volunteered or referred by local practitioners (16 with mTBI).	Self-reported LOC (any duration, range 1–15 min)	between 1–4 months	34.6 (9.2) PTSD; 50.9 (17.3) no PTSD	11 PTSD; 28 no PTSD
	Chamelian, 2006	63 consecutive mild and mod TBI clinic OPs.	mild: GCS 13–15, LOC < 20 min, PTA < 24 hr; mod: GCS 9–12, PTA > 24 hr but < 1 week	6 months	33 (11.7)	56
	Rapoport, 2005	74 mild and mod TBI clinic OPs.	mild: ACRM; mod: GCS 9–12, PTA < 1 week	200.4 (49.5) days (range 122–467)	34.9 (13.1)	NR (NS between dep and non-dep groups)
	Schnabel, 2012	80 mTBI rehab OPs; 80 major depn OPs; 80 HCs.	GCS 13–15 within 30 min, PTA < 24 hr, LOC < 30 min	88 (21) days	38.6 (12.2)	61
	Heitger, 2009	36 mTBI OPs meeting modified post-concussion syndrome criteria; 36 mTBIs with good outcome.	GCS 13–15, disturbance of consciousness < 30 min, PTA < 24 hr	140.2 (50) days PCS; 162.8 (47) days no PCS	38 (14.1) PCS; 37.9 (14.3) no PCS	56

Table 2 *(Continued)*

Recovery Period	First Author, Year	Sample and Setting	TBI definitions	Time post-injury (*SD*)	Mean TBI age (*SD*)	Sex (male%)
Post-acute						
	Sherman, 2000	Archival data from 114 mild and 61 mod-sev TBI litigating clients.	mild: LOC < 1 hr, PTA < 24 hr mod-sev: LOC > 1 hr or PTA > 24 hr	2.5 (2) years	32.8 (12.7)	52
	Ruttan, 2003	Two samples ($n_1 = 72$, $n_2 = 50$) of archival data from mTBIs referred to private practices.	ACRM	39.7 (25.6) months; 20.4 (18.4) months	37.6 (11.3); 37.2 (9.3)	42; 32
	Evered, 2003	Archival data from 129 mTBI clinical OPs with persistent post-concussional disorder.	LOC < 30 min, PTA < 24 hr, GCS ≥ 13, no neurosurgery	16 (13.5) months (range 3 months–7 years)	42 (NR)	54
	Raskin, 1998	148 consecutive mTBIs referred for neuropsychological assessment.	ACRM	21.8 (25.3) months (range 1–214 months)	38.1 (12.4)	46
	Suhr, 2005	Random sample of 53 university students reporting mTBI history.	Self-report of LOC > 1 min but < 30 min	at least 1 year	18.8 (0.7) diagnosis threat; 19.3 (0.9) neutral instructions	42

Note. ACRM = American Congress of Rehabilitation Medicine (1993) criteria for mTBI including LOC < 30 min, PTA < 24 hr and GCS score of 13–15; C = control; CT = computed tomography; dep = depressed; depn = depression; ED = emergency department; GCS = Glasgow Coma Scale; HC = healthy control; LOC = loss of consciousness; mod = moderate; mTBI = mild traumatic brain injury; MVA = motor vehicle accident; NR = not reported; NS = non-significant; nsm = non-smoking; OI = orthopedically injured; OP = outpatient; PCS = post-concussion syndrome; PTA = post-traumatic amnesia; PTSD = post-traumatic stress disorder; rehab = rehabilitation; sev = severe; sm = smoking; TBI = traumatic brain injury; UI = uninjured.

		Titles/ abstracts	Full- text
Not human		82	0
Not adult		115	10
Not English		5	0
Not restricted to mTBI		210	50
Not empirical		520	12
Lack of diagnostic data		0	3
Military		116	13
No psychological and/or cognitive data		447	66
No analysis of relationship		11	82
	Total	1506	236

Total records identified through search: 4460 → Duplicates removed: 2701

Titles/abstracts screened: 1759 → Records excluded: 1506

Full-text articles assessed for eligibility: 253 → Articles excluded: 236

Articles eligible to be included in review: 17

Figure 1. Flow of articles through screening process. mTBI = mild traumatic brain injury.

Table 3

Critical Appraisal Tool (CAT) Scores for each Study

First Author, Year	CAT Item														Total
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	
Ghaffar, 2006	1	1	1	1	0.5	0.5	0	1	0.5	0.5	0.5	2	0.5	0.5	10.5
Clarke, 2012	1	1	1	1	0	0	1	1	0.5	0.5	0.5	2	0.5	0.5	10.5
Durazzo, 2013	1	1	1	1	0	0.5	0	1	0.5	0.5	0.5	2	0.5	0.5	10
Preece, 2007	1	1	1	1	0	0.5	0	1	0.5	0.5	0.5	2	0.5	0.5	10
Ruttan, 2003	1	1	1	1	0	0	0	1	1	0.5	0.5	2	0.5	0.5	10
Beaupré, 2012	1	1	1	0.5	0	0	0	1	0.5	0.5	0.5	2	0.5	0.5	9
Sherman, 2000	1	1	1	0.5	0	0	0	1	0.5	0.5	0.5	2	0.5	0.5	9
Batchelor, 1995	1	1	1	1	0	0.5	0	0	0.5	0	0.5	2	0.5	0.5	8.5
Rapoport, 2005	1	1	1	1	0	0	0	0	1	0	0.5	2	0.5	0.5	8.5
Suhr, 2005	1	1	1	1	0	0	0	0	0.5	0.5	0.5	2	0.5	0.5	8.5
Schnabel, 2012	1	1	0	1	0	0	0	1	0.5	0.5	0.5	2	0.5	0.5	8.5
Evered, 2003	1	1	0	0.5	0	0	0	1	0.5	0.5	0.5	2	0.5	0.5	8
Heitger, 2009	1	1	0	1	0	0	0	0	1	0.5	0.5	2	0.5	0.5	8
Hickling, 1998	1	1	0	1	0	0	1	0	0.5	0.5	0	2	0.5	0.5	8
Chamelian, 2006	1	1	1	1	0	0	0	0	1	0	0	2	0.5	0	7.5
Rao, 2010	1	1	0	0	0	0	0	1	1	0.5	0.5	2	0.5	0	7.5
Raskin, 1998	1	1	0	0.5	0	0	0	0	0.5	0.5	0	2	0.5	0.5	6.5

Methodological Quality

Table 3 shows the results of the quality appraisal. No study earned an optimal score of 12; scores applied to the papers ranged from 6.5 to 10.5. According to Heacock et al.'s (1997) classification system, five studies were rated as strong and 12 were rated as moderately strong. The authors of all studies established that there was a gap in the literature (Item 1), clearly stated the research question (Item 2), achieved a sample size of at least 30 participants (Item 12), and discussed the implications of their findings (Item 13). Fifteen papers identified opportunities for future research (Item 14). A common weakness shared by the majority of studies included a lack of a representative sample (Item 5) from a representative setting (Item 6). Only four studies included participants recruited from trauma or ED settings. The remaining studies included participants recruited from a neurosurgical unit ($n = 1$), multiple settings ($n = 3$), outpatient settings ($n = 9$), and a university ($n = 1$). Only two studies included traumatically non-brain injured control groups (Item 7; Clarke, Genat, & Anderson, 2012; Hickling, Gillen, Blanchard, Buckley, & Taylor, 1998). Other areas of weakness included incomplete reporting of methodology (Item 3), statistical power (Item 8), and statistical tests and significance (Item 9). These shortcomings were consistent with those recognized as being problematic in the mTBI literature (Carroll, Cassidy, Holm, et al., 2004). Studies in the strong category were more likely to use designs classified by the NHMRC (2009) as higher levels of evidence, including prospective longitudinal designs (Durazzo et al., 2013; Ghaffar et al., 2006) and case–control designs (Preece & Geffen, 2007). All but one study (Rao et al., 2010) in the moderately strong category were cross-sectional, the lowest level of evidence (NHMRC, 2009).

Study Findings

Key findings from each study are presented in Table 1. Sample, setting, injury, and demographic data are presented in Table 2. Studies are presented according to the time since injury (i.e., the interval between mTBI and assessment) and setting as both of these factors are

known to moderate estimates of neuropsychological outcome following mTBI (Belanger et al., 2005; McCrea et al., 2009). Studies were grouped according to whether the sample was assessed in the acute (≤ 5 days post-injury) to sub-acute (5–30 days post-injury) or post-acute (> 30 days post-injury) recovery period (McCrea et al., 2009).

Acute to sub-acute phase.

Trauma or ED setting. Only two studies assessed patients in the acute to sub-acute stage of recovery (Batchelor, Harvey, & Bryant, 1995; Preece & Geffen, 2007). Preece and Geffen, whose study received a strong methodological rating, employed a case–control design with participants drawn from prospective consecutive ED presentations. Using a neuropsychological battery, they assessed 389 participants including mTBI patients, controls with orthopedic injuries, and uninjured controls. It was not clear whether any of these participants were involved in litigation and the authors did not report using any measures of effort. Thirty mTBI patients either reported receiving a clinical diagnosis of depression in the previous 6 months or endorsed at least moderate levels of depressive symptoms on a self-report questionnaire. Depressed mTBI cases were matched to 30 non-depressed mTBI cases on the basis of injury and demographic variables. The groups completed tests of processing speed and verbal memory within 24 hours of injury. Their performance was compared using univariate analyses of covariance controlling for blood alcohol concentration which differed between groups. Mild TBI patients who reported recent or current depression performed significantly worse on a measure of verbal recognition than did mTBI patients without depression. Comparisons between controls with and without depression did not reveal any significant differences in cognitive performance. Because patients with current versus recent depression were not analyzed separately, the impact of acute depressive symptoms on cognition following mTBI remains unclear.

Batchelor et al. (1995), whose cross-sectional study was rated as moderately strong, prospectively recruited 50 MVA inpatients with mTBI within a week of injury. A subset of

35 mTBI patients completed a modified Stroop task which included an interference condition that required response set shifting. The mTBI participants were slower than 35 healthy controls in completing the standard but not the interference measures. When state anxiety was included as a covariate in a multivariate analysis of covariance (MANCOVA), performance was similar between groups, suggesting that anxiety moderated cognitive performance. It was not clear whether any of the study participants were involved in litigation and the use of effort measures was not reported.

The generalizability of these studies (Batchelor et al., 1995; Preece & Geffen, 2007) is limited due to the use of non-consecutive subsamples that may not have accurately represented each initial pool of mTBI participants. Additionally, Batchelor et al. included mTBI patients with up to 48 hours of PTA. According to current mTBI classification (Carroll, Cassidy, Holm, et al., 2004), their sample may have included patients with more severe TBIs.

Post-acute phase.

Trauma or ED setting. There was only one study in which the authors reported recruiting a consecutive sample using a prospective longitudinal design (Ghaffar et al., 2006). In a strongly rated study, Ghaffar et al. followed up at 6 months 122 mTBI patients from an original sample of 191 patients recruited from EDs in two tertiary trauma centers. All participants were randomized to receive a multidisciplinary follow-up treatment or treatment as usual. The authors reported no influence of treatment group, psychiatric history, or litigation on attrition. At the follow-up conducted 6 months post-injury, mTBI patients who reported any depressive symptoms on the General Health Questionnaire (Goldberg & Hillier, 1979) were compared on a neuropsychological test battery to those who reported no depressive symptoms. After controlling for age, which differed significantly between groups, those with depressive symptoms performed worse than those without depressive symptoms on measures of attention, reaction time, and non-verbal abstract reasoning. Additional analyses

revealed comparable cognitive performance between litigating and non-litigating participants. The authors did not report examining participants' effort.

Durazzo and colleagues (2013), whose study was rated strongly, also used a prospective longitudinal design and recruited mTBI patients from an ED, however, it was not clear whether these patients consisted of consecutive presentations. Nineteen smoking and 25 non-smoking mTBI participants, as well as 20 healthy controls from the community, completed assessments on average 5 weeks and 7 months post-injury. No participant was involved in litigation at either assessment point. Assessment included self-report questionnaires of anxiety and depressive symptoms, and neuropsychological tests of learning and memory, processing speed, working memory, visuospatial skills, and executive skills. The authors did not report using any measures of effort. While controlling for education, estimated premorbid intelligence, and alcohol use, the results from MANCOVAs indicated there were no significant relationships between symptoms of depression and anxiety and mean performance in any of the cognitive domains at either assessment point. Similarly, depressive and anxiety symptoms were not associated with the degree of change in cognitive performance from the first to second assessment. Given the modest sample size and the number of included variables, it is possible that the analyses had insufficient statistical power to detect the effects of depression and/or anxiety.

Neurosurgical setting. Clarke and colleagues (2012), whose cross-sectional study received a strong rating, recruited mTBI patients who had been admitted to a neurosurgical unit 3 to 12 months prior. Twenty-one mTBI patients were compared to 19 spinal injury patients without brain injury and 20 healthy university students. It was not clear whether any participants were involved in litigation at the time of the assessment and the use of effort measures was not reported. Among mTBI patients, an index reflecting mean performance on attention, working memory, processing speed, memory, and verbal fluency measures was significantly correlated (Pearson's *r*) with an index reflecting mean responses on depression,

anxiety, and neuroticism self-report questionnaires. Greater distress was correlated with worse cognitive performance. Those indices were not significantly correlated among the spinal and healthy control groups.

Multiple settings. A cross-sectional study by Beaupré, De Guise, and McKerral (2012), which received a moderately strong rating, included mTBI patients from both a neurotrauma unit and an outpatient rehabilitation program. The majority of participants were outpatients. Participants were assessed either 2 months ($n = 15$) or 5 months ($n = 15$) post-injury. Seventeen healthy controls were also assessed. The litigation status of participants and the use of effort measures were not reported. Pearson correlational analyses found no relationships between self-report measures of depression and anxiety and performance on attentional tests in mTBI patients. It is noted, however, that mTBI patients had similar psychological and cognitive results when compared to healthy controls, suggesting a restricted range of results and/or limited sensitivity of the measures. The small number of participants in the study also raises the possibility of inadequate statistical power. Additionally, the authors did not control for the effects of pain, which was reported to be significantly correlated with some of the attentional measures.

Rao et al. (2010), whose longitudinal case–control study also received a moderately strong rating, similarly recruited from both a trauma unit and a brain injury unit. It was unclear whether patients were recruited prospectively or retrospectively and whether any were involved in litigation. The authors did not report whether effort measures were used. Forty-three mTBI participants completed a baseline assessment within 2 weeks of injury and were followed up at 2–3, 6, and 12 months post-injury. Patients who met criteria for new-onset depression according to a structured clinical interview at any follow-up ($n = 8$) were compared to those who were not depressed at any time ($n = 35$). Unpaired *t*-tests revealed no differences between depressed and non-depressed participants in performance on measures of attention, memory, processing speed, or executive functioning at any follow-up assessment.

However, the study may have had limited power to detect differences as only eight participants met criteria for new-onset depression. Additionally, the depressed group were significantly older and had a significantly higher rate of brain lesions (frontal subdural hematoma), both of which may have impacted cognitive performance. Forty-two of the 43 participants underwent brain surgery. This number is higher than the reported rate of neurosurgical intervention in mTBI (Borg et al., 2004). Based on current criteria (Carroll, Cassidy, Holm, et al., 2004), a mTBI classification is not applicable when individuals undergo neurosurgery. Thus, most of the participants in the study likely sustained more severe TBIs and the results may have limited external validity regarding mTBI outcomes.

Hickling and colleagues (1998) also recruited from multiple settings. In their cross-sectional study, which was rated as moderately strong, Hickling et al. recruited 107 participants who were referred from local practitioners after seeking medical attention following involvement in an MVA or who were self-referred via local advertising. Participants were classified into injury groups based on whether they reported no head injury, whiplash only, whiplash and striking their head, or LOC (which ranged from 1 to 15 minutes). They were further classified according to whether or not they met diagnostic criteria for PTSD based on a structured clinical interview. These groups were compared on their performance on neuropsychological tests of verbal memory, attention, processing speed, executive functioning, and motor skills. A multivariate analysis of variance found no interaction between injury group, PTSD diagnosis, and cognitive performance. Exploratory univariate analyses of variance also revealed no significant differences between those with and without PTSD among the 16 participants who reported LOC. The authors reported that some participants were involved in litigation at the time of their assessment, however, the impact of this factor on results was not investigated. The use of effort measures was not reported. Additionally, reliance on participants' subjective reports of injury parameters such as LOC may have compromised the reliability of mTBI diagnosis (Ruff et al., 2009).

Outpatient settings. Eight studies included mTBI participants who had been recruited from outpatient settings and assessed at least one month post-injury (Chamelian & Feinstein, 2006; Evered, Ruff, Baldo, & Isomura, 2003; Heitger et al., 2009; Rapoport, McCullagh, Shammi, & Feinstein, 2005; Raskin, Mateer, & Tweeten, 1998; Ruttan & Heinrichs, 2003; Schnabel & Kydd, 2012; Sherman, Strauss, Slick, & Spellacy, 2000). All of these studies used cross-sectional designs, the lowest level of evidence (NHMRC, 2009). In terms of methodology, all but one (Ruttan & Heinrichs, 2003) received moderately strong ratings. Many used convenience samples or archival data from patients seen in TBI clinics or private practice for assessment, rehabilitation, or medicolegal purposes. Five studies indicated that participants were involved in litigation or compensation (Evered et al., 2003; Raskin et al., 1998; Ruttan & Heinrichs, 2003; Schnabel & Kydd, 2012; Sherman et al., 2000). The authors of only one study (Heitger et al., 2009) confirmed that participants were not involved in compensation or legal disputes that could influence motivation. It was unclear whether the two remaining studies included participants involved in litigation or compensation (Chamelian & Feinstein, 2006; Rapoport et al., 2005). The authors of only four studies reported the use of formal measures of effort (Chamelian & Feinstein, 2006; Evered et al., 2003; Schnabel & Kydd, 2012; Sherman et al., 2000). The limited generalizability of these outpatient studies is reflected in the older mean age of participants and fewer male participants compared to studies that recruited from trauma or ED settings (see Table 2), as well as epidemiological estimates of mTBI (Cassidy et al., 2004; Feigin et al., 2013; Leibson et al., 2011).

Of these eight outpatient studies, five revealed significant associations between psychological distress and cognition (Chamelian & Feinstein, 2006; Evered et al., 2003; Rapoport et al., 2005; Ruttan & Heinrichs, 2003; Sherman et al., 2000). In all five studies, greater distress was associated with lower cognitive performance. Only two of these studies screened participants for involvement in litigation and excluded those demonstrating

suboptimal effort (Evered et al., 2003; Sherman et al., 2000). Consequently, it remains possible that the results of some of these studies were confounded by the effects of litigation and/or suboptimal effort (Belanger et al., 2005; Dikmen & Levin, 1993). These results have limited external validity and may apply only to mTBI patients who continue to be symptomatic or who are involved in litigation.

University setting. Suhr and Gunstad (2005), whose cross-sectional study received a moderately strong rating, randomly selected a subgroup from a larger group of university students who screened positive for a history of mTBI at least 12 months prior. None of the students were involved in litigation at the time of assessment. Performance on an effort measure was found to be unrelated to performance on the cognitive tasks. The authors found no relationship of self-reported depression or anxiety to performance on tasks assessing attention, processing speed, memory, and executive functioning. Suhr and Gunstad acknowledged their null findings may have been due to milder levels of injury (no participant reported PTA of more than 30 minutes) and/or minimal levels of reported distress (no participant reported more than mild depressive symptoms). Generalizability of the results was limited because the sample consisted of relatively young, healthy individuals attending university. This study also relied on participants' subjective report of history of mTBI, which may have reduced diagnostic reliability.

Discussion

This paper presents the results from the first systematic review to identify and evaluate the existing evidence regarding the relationship between psychological distress and cognitive outcome following mTBI in adults. Seventeen studies met inclusion criteria. Study design and methodological quality were evaluated based on a hierarchy of evidence (NHMRC, 2009) and a critical appraisal tool (Heacock et al., 1997). Five studies were rated as strong and 12 were rated as moderately strong. The majority of studies were cross-sectional; only two studies used prospective longitudinal designs. Application of the critical appraisal tool

revealed widespread use of non-representative samples and settings. Only two studies included a traumatically non-brain injured control group. Incomplete reporting of design and methodology was common. Additionally, several studies used small samples, and many did not consider the impact of litigation, suboptimal effort, or other potentially confounding variables (such as age or concurrent pain) on measured outcomes. The impact of litigation and effort on the results of these studies remains unknown.

The two studies conducted in the acute to sub-acute phase used case–control (Preece & Geffen, 2007) and cross-sectional (Batchelor et al., 1995) designs. The results suggest an influence of pre-existing depression (Preece & Geffen, 2007) and state anxiety (Batchelor et al., 1995) on verbal recognition and speeded attentional performance, respectively. The results of the two prospective longitudinal studies conducted in the post-acute recovery period were inconsistent (Durazzo et al., 2013; Ghaffar et al., 2006). The results of Ghaffar et al. (2006), who conducted the only prospective longitudinal study of consecutive trauma admissions using a relatively large sample, suggest lower cognitive performance on measures of attention, reaction time, and non-verbal abstract reasoning in mTBI patients reporting depressive symptoms at 6 months post-injury. Durazzo et al. (2009) found no associations of self-reported depression or anxiety with cognitive performance in mTBI participants at 5 weeks or 7 months post-injury though their analyses may have been underpowered. Although these two prospective post-acute studies addressed litigation status, participants were not screened for suboptimal effort (Demakis, Gervais, & Rohling, 2008; Rohling, Green, Allen, & Iverson, 2002). The two studies that included traumatically non-brain injured control groups (Clarke et al., 2003; Hickling et al., 1998) used cross-sectional designs and produced conflicting results. Of these, the study that received a strong rating (Clarke et al., 2003) suggests that an association between elevated psychological distress and lower cognitive performance may be specific to individuals who have sustained mTBIs.

This systematic review comprises a comprehensive effort to evaluate the existing evidence. Articles published prior to 1995 were deemed less likely to have employed contemporary definitions of brain injury (e.g., ACRM, 1993; Carroll, Cassidy, Holm, et al., 2004) making comparison and integration of the results more difficult. Although this restriction was intended to allow higher quality studies to be included, the possibility of publication bias cannot be dismissed (Rosenthal, 1979). The heterogeneity amongst the methodologies and designs of the reviewed studies precluded statistical integration of the data. This variability likely contributed to the contrasting results among studies.

Although attempts were made to complete a systematic appraisal of the quality of the methodology and design of each study using an appropriate tool (Heacock et al., 1997), it is acknowledged that this tool was not designed to appraise psychological literature. Additionally, the tool's results may partially reflect the comprehensiveness of authors' reporting (Higgins & Altman, 2008; Liberati et al., 2009). However, alternative appraisal tools remain problematic for the current research question due to the variability among the reviewed studies and the fact that most existing tools were developed to evaluate randomized controlled trials or other specific study designs (Katrak, Bialocerkowski, Massy–Westropp, Kumar, & Grimmer, 2004). The strengths of Heacock et al.'s tool include its published psychometric properties and suitability for a wide range of study designs (Crowe & Sheppard, 2011). In addition to methodological quality, the scores also reflect important design features, including the use of representative sampling methods within appropriate settings and the inclusion of traumatically non-brain injured control groups. This allowed assessment of external validity and evaluation of whether the observed relationships may be specific to individuals who sustain mTBIs.

Future research is required to confirm and extend the conclusions of this review. Appraisal of the current evidence highlights the need to recruit consecutive mTBI patients from trauma settings to obtain a broad representative sample (Carroll, Cassidy, Holm, et al.,

2004; Dikmen & Levin, 1993; Larrabee et al., 2013). Prospective longitudinal studies are required to investigate the possible mechanisms underpinning the reported associations between psychological distress and cognitive outcome following mTBI. It is currently unclear whether psychological distress compounds cognitive impairment caused by the mTBI or whether greater mTBI-related cognitive deficits may induce psychological distress. Bidirectional relationships between psychological factors and cognition are also possible. Alternatively, other factors, which could pre-date the mTBI, may cause some individuals to be more vulnerable to experiencing both elevated psychological distress and greater cognitive dysfunction following mTBI. Traumatically non-brain injured controls are also necessary to determine whether the reported relationships between psychological distress and cognitive functioning are specific to mTBI (Dikmen & Levin, 1993; Larrabee et al., 2013).

It is difficult to distinguish the etiology of symptoms following mTBI, such as differentiating between those related to psychological distress versus the sequelae of mTBI (Grigsby & Kaye, 1993; O'Donnell, Creamer, Bryant, Schnyder, & Shalev, 2003). For example, fatigue, insomnia, and concentration difficulties are common in depression (*Diagnostic and Statistical Manual of Mental Disorders* [*DSM*], 5th ed.; American Psychiatric Association [APA], 2013) and in the acute stage following mTBI (Carroll, Cassidy, Peloso, et al., 2004). Future research may consider the symptom overlap between these conditions. Valid structured clinical interviews based on established classification systems (e.g., *DSM,* 5th ed.; APA, 2013) may be useful in this regard. Exploring various forms of distress, such as anxiety and post-traumatic stress as well as depression, will also be valuable as these symptoms often present comorbidly following mTBI (Bryant et al., 2010). Assessment of various cognitive domains is recommended to establish the breadth and consistency of any associations between psychological distress and cognitive functioning. Comprehensive reporting and the use of multivariate statistical analysis to control for potentially moderating variables, such as litigation, effort, and pain, is also indicated.

Overall, the present systematic review raises the possibility that individuals experiencing distress following mTBI, in particular depressive symptoms, may be at risk of greater cognitive impairment. Psychological factors may be important to consider in the interpretation of cognitive performance following mTBI. Rehabilitation efforts may also be enhanced by addressing psychological symptoms as well as cognitive deficits in the acute to sub-acute stages of mTBI recovery. The current evidence is limited in quality and quantity and further research is required to characterize the relationship between psychological distress and cognitive functioning following mTBI.

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Appendix A

Table A1

Critical Appraisal Tool Adapted from Heacock, Koehoorn, & Tan, 1997

Item		Scoring	
1	Does the study identify a gap in the existing literature?	Yes	1
		No/Insuff Info	0
2	Is the research question clearly stated?	Yes	1
		No/Insuff Info	0
3	After reading the methodology section, could the reader repeat the study with confidence?	Yes	1
		No/Insuff Info	0
4	Do the authors state the measurement technique(s)/instrument(s) are valid/reliable, or do they provide information so the reader can investigate the validity and reliability of the measurement technique(s)/instrument(s)?	Yes	1
		Yes, for some but not all	0.5
		No/Insuff Info	0
5	Is the study population representative of the end-user population? (a consecutive series of mTBI patients identified at the time of injury was considered to best represent the *end-user population*)	Yes	0.5
		No/Insuff Info	0
6	Is the study setting representative of the workplace to which the results will be applied? (the term *workplace* was understood to be a Level 1 trauma hospital or emergency department [ED] setting)	Yes	0.5
		No/Insuff Info	0
7	Is there an appropriate control/comparison group? (an appropriate control or comparison group was understood to be a consecutive series of traumatically non-brain injured patients identified at the time of injury)	Yes	1
		No/Insuff Info	0
8	Is there a statement about the sample size or power of the study?	Yes	1
		No/Insuff Info	0
9	Do the authors state the statistical test used and the level of significance or confidence levels achieved?	Yes, test and p value/CI	1
		Yes, only test or only p/CI	0.5
		No/Insuff Info	0
10	Do the authors discuss the limitations or biases of the study design and/or methodology?	Yes	0.5
		No/Insuff Info	0
11	Do the authors discuss the effect of the preceding limitations or biases on the results?	Yes	0.5
		No/Insuff Info	0
12	Do the authors achieve any one of the following: Utilize a study population $N \geq 30$; Conduct non-parametric statistics tests for $N < 30$; Conduct parametric tests for $N < 30$ but explain sample is normally distributed; or, Conduct multivariate tests with 10 times as many subjects as there are independent variables?	Yes, for at least one statement	0.5
		No/Insuff Info for all statements	0
13	Do the authors discuss recommendations of the findings for workers? (the term *workers* was understood to be a hospitalized mTBI population)	Yes	0.5
		No/Insuff Info	0
14	Do the authors identify opportunities for further research based on the current study?	Yes	0.5
		No/Insuff Info	0

Note. Adapted from Heacock, Koehoorn, & Tan, 1997; p. 169.

Chapter 3

Exploring the associations of acute post-traumatic stress, depression, and pain with cognitive functioning in patients with mild traumatic brain injury.

Abstract

Few studies have examined the confounding factors of psychological distress and pain in the assessment of cognitive functioning following mild traumatic brain injury (mTBI). The aim of the current study was to explore whether acute post-traumatic stress, depression, and pain were associated with cognitive performance on measures of attention, memory, processing speed, reaction time, working memory, and verbal fluency during the acute to sub-acute phase following mTBI. Consecutive adult mTBI admissions to a Level 1 trauma hospital were screened for inclusion. Fifty participants completed neuropsychological testing and self-report measures of acute post-traumatic stress, depression, and pain at a mean of 2.87 ($SD =$ 2.32) days post-injury. Canonical correlation analyses revealed significant relationships between psychological factors and performance on a task of attention completed under increasing cognitive demands. Acute post-traumatic stress was associated with lower accuracy scores. Pain and acute post-traumatic stress were unexpectedly associated with higher speed scores under standard conditions but lower speed scores under auditory distraction conditions. In the acute to sub-acute recovery phase following mTBI, there may be complex relationships of acute post-traumatic stress and pain to cognitive functions, particularly attentional processes. It is recommended that comorbid psychological factors be considered in the assessment of cognitive functioning following mTBI in clinical and research settings.

Exploring the Associations of Acute Post-Traumatic Stress, Depression, and Pain with

Cognitive Functioning in Patients with Mild Traumatic Brain Injury.

The investigation of cognitive outcomes of patients following mild traumatic brain injury (mTBI) has revealed that most individuals recover fully without the need for intervention (Carroll, Cassidy, Peloso, et al., 2004; Iverson, 2005; McCrea, 2008). Meta-analytic evidence indicates mild cognitive deficits present on neuropsychological testing in the acute to sub-acute phase of mTBI (defined as the period up to 30 days post-injury; McCrea et al., 2009), which resolve between one to three months post-injury (Belanger, Curtiss, Demery, Lebowitz, & Vanderploeg, 2005; Carroll, Cassidy, Peloso, et al., 2004; Frencham, Fox, & Maybery, 2005; Rohling et al., 2011; Schretlen & Shapiro, 2003). Deficits are typically observed in the domains of attention, processing speed, memory, and executive functioning (Belanger et al., 2005; Carroll, Cassidy, Peloso, et al., 2004; Frencham et al., 2005; Rohling et al., 2011; Schretlen & Shapiro, 2003). Debate continues as to whether a small subset of mTBI patients experience chronic difficulties beyond this period, including ongoing cognitive impairment (Bigler et al., 2013; Pertab, James, & Bigler, 2009; see also Larrabee, Binder, Rohling, & Ploetz, 2013; Rohling et al., 2011).

Psychological symptoms during the acute to sub-acute phase have received comparatively less attention but may also play an important role in symptomatic outcomes of mTBI patients (Meares et al., 2006; 2008; Meares, Shores, Taylor, Batchelor, et al., 2011). Prospective studies of mTBI patients recruited from trauma settings have demonstrated that many patients report significant psychological symptoms, including acute post-traumatic stress (Broomhall et al., 2009; Harvey & Bryant, 1998; Levin et al., 2013; Meares et al., 2006) and depression (Federoff et al., 1992; Meares et al., 2006; 2008) on self-report measures or clinical interview. Pain is also frequently reported by mTBI patients during this period, often related to additional injuries sustained at the same time as the mTBI (Alves, Macchiocchi, & Barth, 1993; Bazarian et al., 1999; Faux, Sheedy, Delaney, & Riopelle, 2011;

Landre, Poppe, Davis, Schmaus, & Hobbs, 2006; Meares et al., 2006; 2008; Ponsford,

Cameron, Fitzgerald, Grant, & Mikocka–Walus, 2011). Pain is now widely acknowledged to

involve a strong affective component (Gatchel, Peng, Peters, Fuchs, & Turk, 2007; Merskey

& Bogduk, 1994; Price, 2000) and is closely associated with psychopathology in both clinical

(Dickens, McGowan, Clark–Carter, & Creed, 2002; Fishbain, 2013; Linton, 2000) and

population-based samples (Gerhardt et al., 2011; L. J. Williams, Pasco, Jacka, Dodd, & Berk,

2012). Like psychological symptoms, pain during the acute to sub-acute recovery period has

been linked to symptomatic outcomes in mTBI (Landre et al., 2006; Meares et al., 2008;

Meares, Shores, Taylor, Batchelor, et al., 2011). Pain may also be related to emotional

complaints in the post-acute recovery period (Jamora, Schroeder, & Ruff, 2013).

Despite the frequency at which both psychological symptoms and pain are reported,

and longstanding recognition that both may confound the neuropsychological assessment of

mTBI patients (Alexander, 1995; Carroll, Cassidy, Peloso, et al., 2004; Dikmen & Levin,

1993; Larrabee et al., 2013; E. L. Moore, Terryberry–Spohr, & Hope, 2006), few studies have

examined whether psychological distress and pain are related to cognitive outcome following

mTBI (Carroll, Cassidy, Peloso, et al., 2004; Jamora et al., 2013; E. L. Moore et al., 2006).

This is surprising given the large evidence base demonstrating effects of clinical and sub-

clinical psychological symptoms on cognitive performance in non-brain injured samples

(Andrews & Thomson, 2009; Castaneda, Tuulio–Henriksson, Marttunen, Suvisaari, &

Lönnqvist, 2008; Derakshan & Eysenck, 2009; Eysenck, Derakshan, Santos, & Calvo, 2007;

Johnsen, & Asbjørnsen, 2008; Lee, Hermens, Porter, & Redoblado–Hodge, 2012; Salthouse,

2012). Accumulating evidence suggests that pain may also impact cognitive functioning

(Etherton, Bianchini, Heinly, & Greve, 2006; Hart, Martelli, & Zasler, 2000; D. J. Moore,

Keogh, & Eccleston, 2013; Moriarty, McGuire, & Finn, 2011; Nicholson, 2000; Sanchez,

2011). However, existing research in this area is constrained by methodological difficulties.

Experimentally induced pain may be less distressing and is typically shorter in duration than

pain experienced in a real-world setting (Edens & Gil, 1995; Gagliese, 2007; Patil, Apfelbaum, & Zacny, 1995). Chronic pain studies are also problematic because these samples regularly present with psychological comorbidities that may confound results (Hart et al., 2000; Nicholson, 2000).

In addition to the small number of studies addressing the relationships of psychological distress and pain to cognition following mTBI, the quality of these studies is also limited. These design and methodological issues are common in mTBI research (Carroll, Cassidy, Holm, Kraus, & Coronado, 2004; Dikmen & Levin, 1993). Such weaknesses include the retrospective recruitment of unrepresentative, selected samples that are comprised of symptomatic and/or litigating participants, and inadequate consideration of confounding variables (e.g., effort; Carroll, Cassidy, Holm, et al., 2004). To the author's knowledge, only one prospective longitudinal study of a consecutive trauma cohort has investigated this issue (Ghaffar, McCullagh, Ouchterlony, & Feinstein, 2006). Ghaffar et al. reported that depressive symptoms were related to lower performance on measures of attention, reaction time, and non-verbal abstract reasoning in mTBI patients assessed 6 months post-injury. In the acute to sub-acute phase, only two studies have examined these relationships (Batchelor, Harvey, & Bryant, 1995; Preece & Geffen, 2007). Preece and Geffen (2007) reported that, among mTBI participants assessed within 24 hours of injury, pre-existing depression (defined by either self-report of a clinical diagnosis of depression within the last 6 months or moderate depressive symptomatology on a standardized questionnaire) was associated with worse performance on a measure of verbal memory recognition. Among hospitalized mTBI patients assessed approximately six days post-injury, Batchelor and colleagues (1995) described state anxiety as moderating performance on a modified version of the Stroop test. None of the abovementioned studies controlled for the effects of comorbid psychopathology or pain, rendering it possible that those factors contributed to the results.

Four studies have examined the effect of pain on cognitive functioning following mTBI (Beaupré, De Guise, & McKerral, 2012; Jamora et al., 2013; Landre et al., 2006; Tsushima & Newbill, 1996), three of which detected no significant association between pain and cognitive performance (Jamora et al., 2013; Landre et al., 2006; Tsushima & Newbill, 1996). Because two of those studies recruited participants who had been referred for neuropsychological assessment on average one to two years post-injury (Jamora et al., 2013; Tsushima & Newbill, 1996), their results may not generalize to the wider population of mTBI patients who present to acute trauma services. While Landre et al. prospectively recruited consecutive trauma patients, they analyzed data from a group comprised of both non-brain injured and mTBI patients, precluding conclusions regarding the association of pain with cognition in mTBI patients specifically. In a sample of rehabilitation outpatients who were assessed from 1 to 7 months post-injury, Beaupré et al. (2012) found mixed associations between pain and attentional performance. Greater pain was associated with fewer hits on a visual selective attention task from the Test of Everyday Attention (TEA; Robertson, Ward, Ridgeway, & Nimmo–Smith, 1994) but faster response time per target on another TEA visual selective attention test. In contrast, pain was not significantly related to performance on the Ruff 2 & 7 Selective Attention Test (Ruff & Allen, 1996) in Beaupré et al.'s sample. None of the abovementioned mTBI studies investigating pain controlled for comorbid distress. Thus, the association between pain and cognitive functioning following mTBI remains unclear, particularly in the acute to sub-acute period.

The aim of the current study was to examine whether psychological factors, namely psychological distress and pain, were associated with cognitive functioning in trauma patients in the acute to sub-acute phase following mTBI. Specifically, the associations were explored between self-report measures of acute post-traumatic stress, depression, and pain, and cognitive performance on neuropsychological measures of attention, memory, processing speed, reaction time, working memory, and verbal fluency. It was hypothesized that acute

post-traumatic stress, depression, and pain would be associated with lower performance on neuropsychological measures.

Method

Sample

Consecutive trauma admissions to a Level 1 trauma hospital were screened for inclusion from April 2011 to July 2012. The current sample of mTBI patients was recruited as a part of a larger study that included complicated mTBI and moderate TBI patients. For the purpose of the current study, only participants with uncomplicated mTBI were included. Patients were eligible to participate if they had sustained a mTBI according to World Health Organization (WHO) diagnostic criteria (Carroll, Cassidy, Holm, et al., 2004), which includes post-traumatic amnesia (PTA) of less than 24 hours duration, a Glasgow Coma Scale (GCS) score of 13 to 15 within 30 minutes of injury or upon presentation for healthcare, and a loss of consciousness (LOC) for no longer than 30 minutes. Additional inclusion criteria included (a) aged between 18 and 65 years, (b) admission to hospital within 24 hours of injury, (c) assessment within 14 days of injury, and (d) sufficient English language comprehension and fluency to enable valid test administration. Exclusion criteria included (a) acute intracranial pathology, (b) depressed skull fracture on neuroimaging (D. H. Williams, Levin, & Eisenberg, 1990), (c) pre-existing cognitive impairment, (d) an IQ of less than 70, (e) psychotic illness, (f) physical injury as a result of self-harm, (g) suicidality, (h) medically unable to participate (i.e., physical injuries prevented participation in the assessment), (i) the subject of forensic investigation, (j) an interstate or overseas visitor (to ensure availability for follow-up assessments), (k) pregnancy (to avoid possible confounds with pregnancy-related cognitive deficits; De Groot, Vuurman, Hornstra, & Jolles, 2006), or (l) suboptimal effort identified on the Computerized Test of Information Processing (CTIP; Tombaugh & Rees, 2008) and the California Verbal Learning Test, 2nd ed. (CVLT-II, Delis, Kaplan, Kramer, & Ober, 2000;

Heilbronner et al., 2009; Larrabee, 2008; Slick, Sherman, & Iverson, 1999; Victor, Boone, Serpa, Buehler, & Ziegler, 2009).

Of 3471 consecutive trauma admissions, 98 patients met inclusion criteria (see Figure 1). Fifty-seven (58.2%) patients provided written consent and participated in the study.

Measures

The Acute Stress Disorder Scale (ASDS) is a 19-item self-report questionnaire and is a reliable and valid measure of acute stress disorder symptoms (Bryant, Moulds, & Guthrie, 2000). A total score was obtained by summing all items with the exception of the amnesia item, which may be confounded by patients' experience of PTA, psychogenic amnesia, or the effect of opioids (Bryant & Harvey, 1999; O'Donnell, Creamer, Bryant, Schnyder, & Shalev, 2003).

The total severity score of the ASDS was used rather than a categorical diagnosis in order to preserve sensitivity and statistical power. Additionally, research has indicated that dimensional measures, rather than the cluster-based diagnoses (e.g., *Diagnostic and Statistical Manual of Mental Disorders* [*DSM*], 4th ed., text rev.; American Psychiatric Association [APA], 2000), may more accurately reflect the range of psychological responses among individuals (A. M. Ruscio & Ruscio, 2002; A. M. Ruscio, Ruscio, & Keane, 2002; J. Ruscio & Ruscio, 2000; Slade & Andrews, 2005), including those that follow mTBI (E. L. Moore et al., 2006) and trauma (Bryant, Friedman, Speigel, Ursano, & Strain, 2011). The use of a total score also aligns with recent revisions to the diagnostic classification of acute stress disorder (*DSM*, 5th ed.; APA, 2013).

Participants completed the 21-item version of the Depression Anxiety Stress Scale (DASS-21; Lovibond & Lovibond, 1995), a reliable and valid measure of depression, anxiety, and stress in TBI (Antony, Bieling, Cox, Enns, & Swinson, 1998; Dahm, Wong, & Ponsford, 2013; Henry & Crawford, 2005; Lovibond & Lovibond, 1995; Ng et al., 2007). The depression subscale (DASS-D) was used. This subscale excludes somatic symptoms which
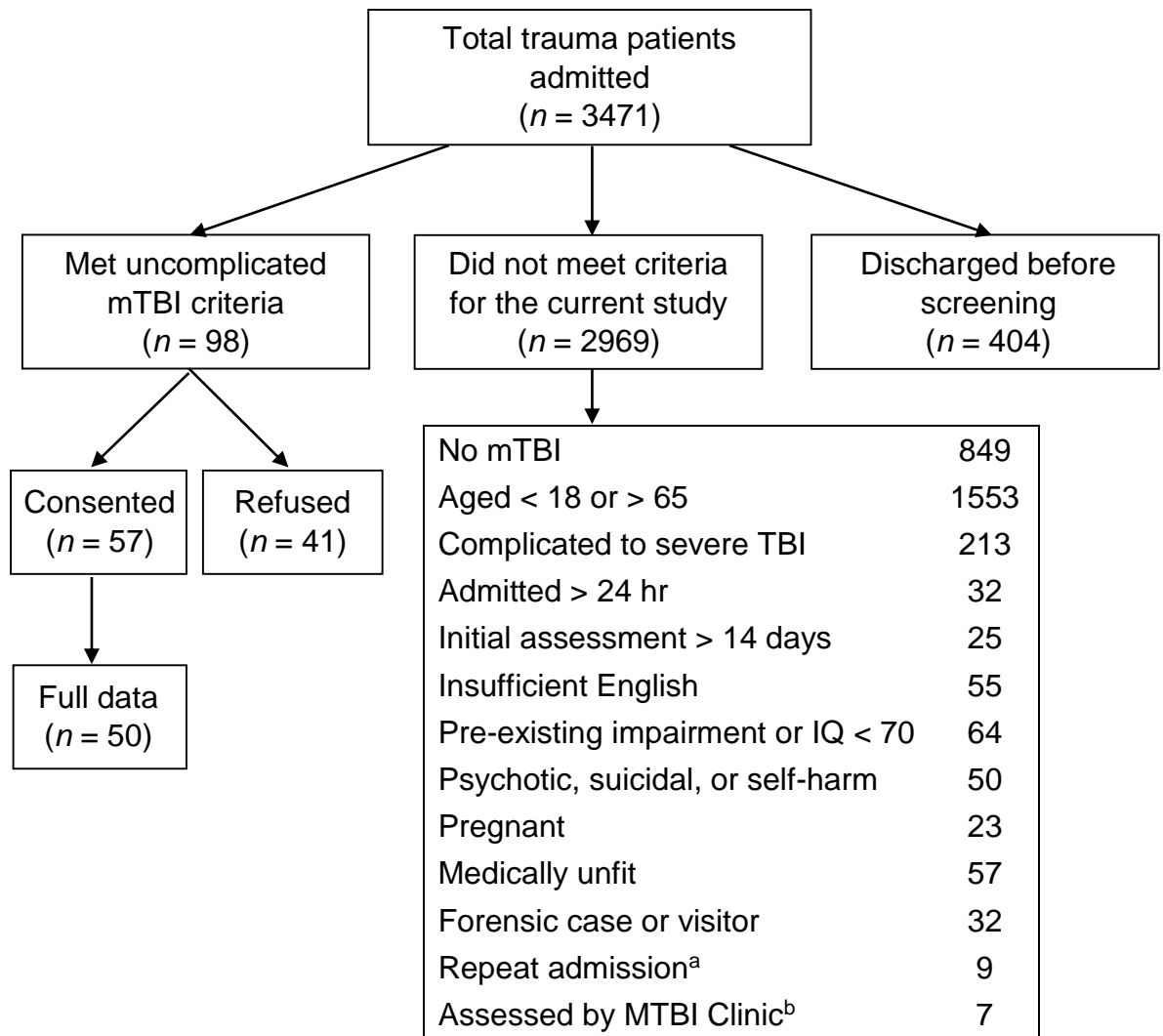
Figure 1. Flow of trauma admissions through the screening, recruitment, and assessment

process. mTBI = mild traumatic brain injury; TBI = traumatic brain injury. [a]Patients were

excluded if they were re-admitted for the same injury and had already undergone study

screening. [b]Patients were excluded if they had already undergone a neuropsychological

assessment within the hospital's MTBI Clinic to avoid the possibility of practice effects on

cognitive tasks.

may be confounded by patients' physical injuries. The subscale total score was doubled prior to analysis (Lovibond & Lovibond, 1995).

Participants completed a subjective rating of their current overall pain intensity on an 11-point numerical rating scale ranging from 0 (*no pain*) to 10 (*pain as bad as it could be*; Jensen & Karoly, 2011). Numerical pain rating scales are reliable and valid and have been recommended for the assessment of pain intensity in clinical and research settings (Good et al., 2001; Hjermstad et al., 2011; Jensen & Karoly, 2011).

The CVLT-II is a valid and reliable measure of verbal learning and memory (Delis et al., 2000) that involves learning a list of words over five trials. Tests of memory may be among the most sensitive to mTBI-related deficits within the first 7 days of injury (Rohling et al., 2011). The sum of learning trials *T*-score and the long-delay free recall (LDFR) trial *z*-score were used in the analysis (Delis et al., 2000). Suboptimal effort on the CVLT-II was defined as performance at or below raw score cut-offs of 34 on the sum of the learning trial and 6 on the long delay cued-recall trial (Millis, Putnam, Adams, & Ricker, 1995).

The extended Ruff 2 & 7 procedure was administered according to the method of Cicerone (1996). In the original Ruff 2 & 7 Selective Attention Test (Ruff & Allen, 1996), individuals mark as many targets as possible within a limited period of time. Targets (the numbers 2 and 7) are interspersed among distractors of random letters or digits. Cicerone's (1996) procedure involves completing 10 trials under *standard* (STD) conditions, 10 trials with a *non-relevant distraction* (NRD) consisting of a radio playing in the background, 10 trials with a *relevant distraction* (RD), followed by another 10 trials under STD conditions. The RD condition consists of a dual-task in which participants mark targets in addition to answering simple arithmetic problems presented every 5 seconds. Each condition yields two scores: a speed score consisting of the number of correctly marked targets, and an accuracy score consisting of the percentage of correct hits. The number of arithmetic errors was subtracted from the total correct hits prior to calculating speed and accuracy scores in the RD

condition (Cicerone, 1996). Analysis revealed there were no significant differences between early and late STD speed scores, $t(41) = -1.38$, $p = .18$, 95% CI [-13.60, 2.55], nor between early and late STD accuracy scores, $t(41) = 1.51$, $p = .14$, 95% CI [-0.003, 0.024]. The scores obtained from early and late STD trials were consequently combined to create total STD speed and accuracy scores. The NRD and RD scores were doubled to enable comparability (Cicerone, 1996). The original Ruff 2 & 7, which has high reliability and construct validity (Bate, Mathias, & Crawford, 2001; Ruff & Allen, 1996), measures selective and sustained attention (Ruff & Allen, 1996). The RD condition may additionally require the ability to shift attention and actively coordinate attentional resources (Cicerone, 1996). Cicerone (1996) found that the extended version was more sensitive to the cognitive effects of mTBI than other neuropsychological tests when participants were compared to healthy controls on average 19 months post-injury.

The Symbol Digit Modalities Test (SDMT) is a reliable and valid measure of visual attention and processing speed (Bate et al., 2001; Smith, 1991) that requires individuals to decode unfamiliar symbols according to a key in a specified time period. The SDMT is sensitive to concussion-related deficits (Hinton–Bayre, Geffen, Geffen, McFarland, & Friis, 1999; Iverson, Lovell, & Collins, 2005; Meares et al., 2008). The oral version was administered to minimize the effects of physical injuries on performance. Raw scores were converted into age- and education-adjusted z-scores (Smith, 1991).

The CTIP (Tombaugh & Rees, 2008) measures reaction time (RT) using subtests that differ in the amount of information that needs to be processed. Subtests include simple reaction time (SRT), which involves a response to a single recurring target, choice reaction time (CRT), which involves choosing the correct response when presented with one of two words, and semantic search reaction time (SSRT). The latter requires individuals to decide whether a target word belongs or does not belong to a specified semantic category. Age-adjusted median reaction time percentiles were obtained from each CTIP subtest (Tombaugh

& Rees, 2008). The CTIP has good reliability and validity (Tombaugh & Rees, 2008) and has been found to be sensitive to cognitive deficits following mTBI (Tombaugh, Rees, Stormer, Harrison, & Smith, 2007). Suboptimal effort on this task was defined according to multiple criteria specified by Tombaugh and Rees (2008; Willison & Tombaugh, 2006): (a) an SRT score more than .1 sec slower than the 1st percentile, (b) variability as evidenced by a coefficient of variation score below the 1st percentile for any subtest, and (c) more than four incorrect responses on the CRT or SSRT tests.

Verbal fluency tasks require individuals to orally produce words according to specified restrictions as quickly as possible (Strauss, Sherman, & Spreen, 2006). Letter (F, A, S) and semantic (animal) fluency scores were converted into age-, ethnicity- and education-adjusted T-scores (Heaton, Miller, Taylor, & Grant, 2004). Fluency measures are reliable (Tombaugh, Kozak, & Rees, 1999) and valid (Boone, Pontón, Gorsuch, Gonzáles, & Miller, 1998; Henry & Crawford, 2004) and have been found to be sensitive to the cognitive impairments characterizing mTBI in the first 3 months post-injury (Belanger et al., 2005; Iverson, Franzen, & Lovell, 1999).

The Brown–Peterson Task is a measure of working memory (Brown, 1958; Peterson & Peterson, 1959). Individuals are presented with 3-letter trigrams (e.g., QLX) that they are required to recall following different timed intervals during which they perform an interference task (i.e., counting backwards by 3 over delay intervals of 9-, 18-, or 36-s). Typically, individuals recall fewer letters following longer delays (Anil et al., 2003; Stuss, Stethem, Hugenholtz, & Richard, 1989). Scores consist of the number of correctly recalled letters. Age-adjusted z-scores were calculated (Stuss, Stethem, & Pelchat, 1988). Variants of the test are reliable (Anil et al., 2003; Mertens, Gagnon, Coulombe, & Messier, 2006) and valid (Anil et al., 2003; Boone et al., 1998; Mertens et al., 2006). The task is sensitive to cognitive deficits in the acute to sub-acute period following mTBI (Stuss et al., 1989).

The Test of Premorbid Functioning (TOPF) requires the participant to read aloud a list of irregular words. It is used to estimate premorbid intellectual ability and has evidence of reliability and validity (Holdnack & Drozdick, 2009). A similar measure has shown evidence of validity in a TBI population (Green et al., 2008).

Procedures

Ethical approval was obtained from the Human Research Ethics Committees of Macquarie University and the Western Sydney Local Health Network, in Sydney, Australia. Eligible patients were prospectively identified from weekday lists that included weekend trauma admissions. All patients were screened, and medical records reviewed, to evaluate eligibility according to the inclusion and exclusion criteria. If eligible, patients were invited to participate. All participants provided informed written consent. Participants were cleared from PTA using the Abbreviated Westmead PTA Scale (Meares, Shores, Taylor, Lammél, & Batchelor, 2011) or the Westmead PTA Scale (Shores, Marosszeky, Sandanam, & Batchelor, 1986). Eligible patients who had been discharged were not contacted for screening or assessment due to differences in the assessment settings that may have confounded the results.

Demographic information was obtained on interview. Participants were also asked whether they were seeking compensation or were involved in litigation. An estimate of PTA duration was obtained retrospectively by asking participants to describe their memories following their injury using open-ended questions (Gronwall & Wrightson, 1980; Levin, O'Donnell, & Grossman, 1979). Ambulance and medical records were used to obtain objective information regarding GCS scores, LOC, confusion, disorientation, and other physical injuries. Physical injuries were classified into orthopedic (e.g., fractures, dislocations), soft tissue (e.g., significant lacerations, abrasions, hematomas), internal, or other (e.g., subconjunctival hemorrhage) categories (adapted from Landre et al., 2006). Opioid (morphine, codeine, oxycodone, oxycodone hydrochloride, tramadol hydrochloride,

fentanyl, and methadone) intake in the 24 hours prior to assessment was obtained from

medication charts. Screening and assessments were conducted bedside by four provisional

psychologists undertaking postgraduate training in clinical neuropsychology. Before

screening, participants were randomized (Urbaniak & Plous, 2011) to complete either the

psychological measures prior to cognitive measures or the reverse, to avoid effects of order

and fatigue on performance. The duration of the entire assessment was approximately 2

hours.

Statistical Analysis

Variables in *z*-score format were transformed into *T*-scores using a conversion table

(Strauss et al., 2006). Screening of histograms, normal p-p plots, and box plots revealed that

the ASDS total score, DASS-D score, pain rating, semantic fluency, and CTIP median

reaction time (SRT, CRT, and SSRT conditions) variables were positively skewed. The

CVLT-II LDFR, BP 9-s, and the extended Ruff 2 & 7 Accuracy (STD, NRD, and RD

conditions) scores were negatively skewed. Positively skewed variables were normalized

using square root, logarithmic, or inverse transformations. Negatively skewed variables were

reflected and then transformed using square root or logarithmic functions (Tabachnick &

Fidell, 2013). Transformed scores were used in all analyses except scatterplots of the

untransformed data. Although some univariate outliers remained following transformation,

all cases were retained to preserve statistical power. Exclusion of the outliers did not

significantly change the outcomes of the study. Where applicable, scores were reversed so

that higher scores on all cognitive variables reflected better performance. Transformed ASDS

total scores were also reversed so that higher scores on the psychological distress and pain

variables indicated greater symptomatology. Visual inspection of scatterplots revealed no

systematic departures from the assumption that psychological and cognitive variables were

linearly related.

Patients who consented and those who refused were compared to evaluate any differences in demographic or injury variables using independent sample *t*-tests and chi-square tests with the exception of days of hospitalization which was positively skewed and which was evaluated using the Mann–Whitney *U*-test. Missing data were analyzed for randomness using Little's test (Little, 1988).

The data were analyzed using canonical correlation analysis (CCA) because it permits simultaneous analysis of two sets of variables (Sherry & Henson, 2005). CCA precludes the need for variable sets to be combined into composite scores or analyzed on a bivariate basis, either of which may obscure potentially complex relationships between variable sets (Thompson, 2000). Because the variables within sets were intercorrelated, CCA reduced potential redundancy and false positive findings (Thompson, 2000).

CCA creates pairs of linear combinations from two sets of observed variables (see Stevens, 1992; Thompson, 2000). The linear combination produced from each set of variables is called a *canonical variate* (CV). Together, the first pair of CVs forms a *canonical function* that maximizes the correlation between the CVs. This correlation, known as the *canonical correlation* (symbolized by r_c), is a Pearson *r* that reflects the degree to which the two CVs are related. The *squared canonical correlation* (symbolized by r_c^2) indicates the proportion of shared variance between the two CVs. A second canonical function is derived which also maximizes the correlation between CVs but which is orthogonal to the first canonical function. This process is repeated until the maximum number of canonical functions is reached. Statistical significance of the canonical correlations is hierarchically evaluated using Wilk's lambda (λ) tests. The overall model, which includes all canonical functions, is first tested for significance. The value of $1 - \lambda$ can be interpreted as an effect size, indicating the variance shared by the variable sets across all of the canonical functions (Sherry & Henson, 2005). The first canonical function is then removed and the remaining canonical functions are tested for significance. For each CV, *standardized function*

coefficients reflect the weighting of each variable in *SD* units, analogous to beta weights in multiple regression. *Structure coefficients* (symbolized by r_s) reflect the correlation between the observed variable and its CV. *Squared structure coefficients* (symbolized by r_s^2) reflect the proportion of variance shared between the observed variable and the CV, or alternatively, how much of the observed variable is used in defining the CV.

A series of CCAs was conducted to explore the relationships between a common set of psychological variables and various sets of cognitive variables. The psychological variable set used in each analysis consisted of ASDS total scores, DASS-D scores, and subjective pain ratings. Sets of cognitive variables were formed from each cognitive measure. Individual CCAs for each cognitive measure were selected in favor of a single analysis that included all cognitive tasks in order to maximize the participant-to-variable ratio. The following cognitive variable sets were analyzed: (a) CVLT-II Sum of Learning Trials 1 to 5 *T*-score and CVLT-II LDFR *T*-score, (b) extended Ruff 2 & 7 STD speed score, extended Ruff 2 & 7 NRD speed score, and extended Ruff 2 & 7 RD speed score, (c) extended Ruff 2 & 7 STD accuracy score, extended Ruff 2 & 7 NRD accuracy score, and extended Ruff 2 & 7 RD accuracy score, (d) SDMT oral *T*-score, (e) CTIP SRT median RT percentile, CTIP CRT median RT percentile, and CTIP SSRT median RT percentile, (f) letter and semantic fluency *T*-scores, and, (g) BP 9-s total *T*-score, BP 18-s total *T*-score, and BP 36-s total *T*-score. Extended Ruff 2 & 7 accuracy and speed subsets were not combined in order to maximize the participant-to-variable ratio. For the same reason, additional scores comparing controlled and automatic processing on the extended Ruff 2 & 7 (Cicerone, 1996) were not analyzed. Prior to analysis, the cognitive variables were regressed against age and TOPF standard scores to remove any remaining effects of age and estimated premorbid ability.

The alpha level was set at .05 for all comparisons. Because of the exploratory nature of the research and the small sample size, it was considered more important to preserve the Type II error rate than to adjust alpha for multiple comparisons. Alpha adjustments may be

inappropriate in neuropsychological research when study variables are intercorrelated (Eichstaedt, Kovatch, & Maroof, 2013) and when the overall null hypothesis is not of primary interest (Brandt, 2007; Perneger, 1998). Cohen's (1988) classification of effect sizes was used to aid interpretation, whereby correlation coefficients (r) of .1, .3, and .5, and degrees of shared variance (r^2) of .01, .09, and .25, each correspond to small, medium, and large effects, respectively. This approach was taken because most effect sizes in the mTBI literature report the extent of mean differences between mTBI and comparison groups and, to the author's knowledge, there are no published guidelines regarding correlational or shared variance effect sizes specific to mTBI research.

Results

Table 1 provides descriptive statistics of those who consented and refused. No significant differences were found between those who consented and refused in terms of age, $t(94) = -0.70$, $p = .49$, 95% CI [-6.89, 3.31]; gender, $\chi^2(1, 98) < 0.01$, $p = .98$, $\Phi < -.01$; days of hospitalization, Mann–Whitney $U = 1065$, $z = -0.75$, $p = .45$; orthopedic injuries, $\chi^2(1, 97) = 0.55$, $p = .46$, $\Phi = -.08$; soft tissue injuries, $\chi^2(1, 97) < 0.01$, $p = .94$, $\Phi < .01$; internal injuries, $\chi^2(1, 97) = 1.12$, $p = .29$, $\Phi = -.11$; or other injuries $\chi^2(1, 97) = 1.63$, $p = .20$, $\Phi = .13$. No participant was excluded on the basis of suboptimal effort.

A number of variables had missing data. Seven cases did not complete the TOPF; six were missing because the test was introduced after the study commenced and one was missing because the participant was discharged prior to completing the assessment. The maximum number of cases in each CCA was 50. Overall, the data were missing at random, Little's test, $\chi^2(106) = 104.63$, $p = .52$. All cases were consequently retained to preserve statistical power (i.e., listwise deletion was not employed).

Participants had a mean age of 36.70 ($SD = 13.86$) years (range: 19–62) and the majority were male (82%). Most participants were born in Australia (64%) and spoke English as their first language (80%). Participants had a mean of 12.02 ($SD = 2.45$) years of

Table 1

Descriptive Statistics of Patients who Participated versus Refused

Variable	Participants (*n* = 57)		Refusers (*n* = 41)	
	M (*SD*)	*n* (%)	*M* (*SD*)	*n* (%)
Age	37.2 (13.8)		35.4 (11.6)	
Days of hospitalization	6.2 (0.8)		6.9 (1.0)	
Male		46 (80.7)		33 (80.5)
Orthopedic injuries		43 (75.4)		34 (82.9)
Soft tissue injuries		25 (43.9)		18 (43.9)
Internal injuries		10 (17.5)		11 (26.8)
Other injuries		7 (12.3)		2 (4.9)

education (range: 7–18) and the majority were employed (82%). The mean TOPF standard

score was 94.44 (SD = 12.44). The most common mechanisms of injury were involvement in

a motor vehicle accident (48%), fall (24%), and cycling accident (16%). Participants were

assessed a mean 2.87 (SD = 2.32) days post-injury (range: 0.60–11.93) and were hospitalized

for a median of 4 days (range: 1–26). The majority of participants (n = 32; 64%) had a GCS

score of 15 upon presentation while 13 participants (26%) had a score of 14 and two (4%) had

a score of 13. Three participants (6%) did not have GCS records. PTA duration was

estimated to be less than 5 minutes in 16 participants (32%), 6 to 60 minutes in 10 (20%), 61

minutes to 12 hours in 18 (36%), and 12 to 24 hours in six participants (12%). Forty-five

participants (90%) underwent computed tomography brain scans, all of which were reported

as normal. Orthopedic injuries were classified as present in 38 participants (76%), soft tissue

injuries in 23 (46%), internal injuries in eight (16%), and other injuries in four participants

(8%). Forty-two participants (84%) had been administered at least one type of opioid in the

24 hours prior to the assessment. Twelve participants (24%) had more than one type of

opioid. Seven participants (14%) were seeking compensation. Thirty-two (64%) were not,

another 11 (22%) were unsure if they would seek compensation. Two (4%) participants were

involved in litigation, 42 (84%) were not and 6 (12%) were unsure if they were involved in

any litigation. Untransformed and transformed mean scores on the psychological and

cognitive measures of interest are provided in Table 2.

 CCAs were performed between the pairs of psychological and cognitive variable sets.

Results of significance testing for each CCA are displayed in Table 3. Significant overall

tests were obtained in the CCAs conducted on the psychological variables and the extended

Ruff 2 & 7 speed measures, Wilk's λ = .577, $F(9, 87.77)$ = 2.47, p = .015, and the extended

Ruff 2 & 7 accuracy measures, Wilk's λ = .497, $F(9, 87.77)$ = 3.24, p =.002. The degree of

overall shared variance $(1 - \lambda)$ was large in both CCAs (42.3% and 50.3% in speed and

accuracy CCAs, respectively). Because the overall test was the only significant test for each

Table 2

Untransformed and Transformed Mean Scores on Psychological and Cognitive Measures

Measure	n	M	SD	M tfd	SD tfd
ASDS total[a]	50	35.44	14.93	-0.03	0.01
DASS-D subscale[b]	50	6.04	9.05	0.54	0.52
Subjective pain rating[c]	50	3.94	2.11	2.17	0.49
CVLT-II Sum Trials 1 to 5 *T*-score	50	50.04	11.26		
CVLT-II Long Delay Free Recall *T*-score[d]	50	44.98	12.20	-4.37	1.42
Ext Ruff 2 & 7 Speed STD	42	229.74	53.60		
Ext Ruff 2 & 7 Speed NRD	42	227.57	50.99		
Ext Ruff 2 & 7 Speed RD	42	164.90	54.09		
Ext Ruff 2 & 7 Accuracy STD[e]	42	92.20	6.73	-.75	.36
Ext Ruff 2 & 7 Accuracy NRD[e]	42	92.57	7.64	-.71	.39
Ext Ruff 2 & 7 Accuracy RD[e]	42	87.18	11.50	-.99	.39
SDMT oral *T*-score	49	44.87	12.81		
CTIP SRT median RT percentile[b]	45	17.17	25.16	.77	.69
CTIP CRT median RT percentile[b]	45	9.44	18.47	.46	.61
CTIP SSRT median RT percentile[b]	45	14.40	21.74	.65	.71
Letter fluency *T*-score	49	46.09	10.59		
Semantic fluency *T*-score[b]	49	50.86	14.07	1.69	0.12
BP 9-s *T*-score[d]	46	49.56	11.69	-3.77	1.51
BP 18-s *T*-score	46	49.83	11.37		
BP 36-s *T*-score	46	52.95	10.36		

Note. ASDS = Acute Stress Disorder Scale; BP = Brown–Peterson task; CRT = choice reaction time; CTIP = Computerized Test of Information Processing; CVLT-II = California Verbal Learning Test – 2nd ed.; DASS-D = Depression Anxiety Stress Scale 21-item depression subscale; Ext Ruff 2 & 7 = extended version of the Ruff 2 & 7 Selective Attention Test; NRD = non-relevant distraction condition; RD = relevant distraction condition; RT = reaction time; SDMT = Symbol Digit Modalities Test; SRT = simple reaction time; SSRT = semantic search reaction time; STD = standard condition; tfd = transformed.

[a]Reflected then transformed using inverse function. [b]Transformed using logarithmic function. [c]Transformed using square root function. [d]Reflected then transformed using square root function. [e]Reflected then transformed using logarithmic function. (Tabachnick & Fidell, 2013).

Table 3

Canonical Correlations and Results of Hierarchical Significance Testing

Cognitive variable set[a]	n	r_c[b]	r_c^2	Wilk's λ	F	df_1	df_2	p-value
CVLT-II Sum, LDFR	50	.27	7.17%	0.92	0.66	6	90	.68
		.11	1.22%	0.99	0.28	2	46	.75
Ext Ruff 2 & 7 STD Speed, NRD Speed, RD Speed	42	.64	40.47%	0.58	2.47	9	88	.015
		.15	2.37%	0.97	0.29	4	74	.88
		.08	0.70%	0.99	0.27	1	38	.61
Ext Ruff 2 & 7 STD Accuracy, NRD Accuracy, RD Accuracy	42	.68	45.78%	0.50	3.24	9	88	.002
		.26	6.70%	0.92	0.82	4	74	.52
		.13	1.71%	0.98	0.66	1	38	.42
SDMT oral	49	.16	2.48%	0.98	0.38	3	45	.77
CTIP SRT, CRT, SSRT	45	.50	25.12%	0.69	1.77	9	95	.08
		.29	8.23%	0.92	0.91	4	80	.47
		.05	0.26%	1.00	0.11	1	41	.75
Letter fluency, semantic fluency	49	.36	13.05%	0.84	1.32	6	88	.26
		.18	3.22%	0.97	0.75	2	45	.48
BP 9-s, 18-s, 36-s	46	.37	13.35%	0.79	1.12	9	98	.35
		.27	7.30%	0.91	1.02	4	82	.40
		.15	2.11%	0.98	0.90	1	42	.35

Note. BP = Brown–Peterson task; CRT = choice reaction time; CTIP = Computerized Test of Information Processing; CVLT-II = California Verbal Learning Test – 2nd ed.; Ext Ruff 2 & 7 = extended version of the Ruff 2 & 7 Selective Attention Test; LDFR = long delay free recall; NRD = non-relevant distraction condition; r_c = canonical correlation; r_c^2 = squared canonical correlation; RD = relevant distraction condition; SDMT = Symbol Digit Modalities Test; SRT = simple reaction time; SSRT = semantic search reaction time; STD = standard condition; Sum = Sum of trials 1–5.
[a]For every analysis, the psychological variable set consisted of Acute Stress Disorder Scale total score, Depression Anxiety Stress Scale 21-item depression subscale score, and subjective pain rating. [b]Listed in descending order for each analysis (i.e., within each cognitive variable set).

of these analyses, only the largest canonical correlation in each analysis was interpreted (Stevens, 1992; Tabachnick & Fidell, 2013). The standardized function coefficients, structure coefficients, and squared structure coefficients of the significant canonical correlations are presented in Figure 2.

Extended Ruff 2 & 7 Speed

The CVs that were derived from the psychological variables and the extended Ruff 2 & 7 speed variables shared a large degree of variance (40.47%; Figure 2a). Inspection of the psychological standardized function coefficients (displayed within parentheses in variable boxes in Figure 2) indicated that all variables contributed to the prediction of the psychological CV. The structure coefficients (displayed adjacent to arrows in Figure 2), however, indicated that pain ($r_s = .80$) and acute post-traumatic stress ($r_s = .56$) correlated strongly with the psychological CV, whereas depression showed a weak correlation ($r_s = -.07$). This pattern of results suggests that higher levels of pain, as well as greater severity of acute post-traumatic stress symptoms, were associated with higher scores on the psychological CV. The moderate size of the depression function coefficient but low structure coefficient may reflect a suppressor effect (Courville & Thompson, 2001; Thompson, 2000). That is, although depression showed minimal correlation with the psychological CV itself, it may have aided the prediction of the CV (resulting in a non-negligible function coefficient) by removing redundancy amongst the psychological variables.

In terms of speeded performance, all conditions (STD, NRD, and RD) showed sizeable standardized function coefficients, suggesting that speed scores in all conditions contributed to the prediction of the cognitive CV. The structure coefficients (and squared values) indicated that STD speed scores were the most strongly correlated with cognitive CV scores ($r_s = .56$), whereas NRD and RD speed scores shared less variance (15.21% and 1%, respectively) with the cognitive CV. Overall, higher STD speed scores were associated with
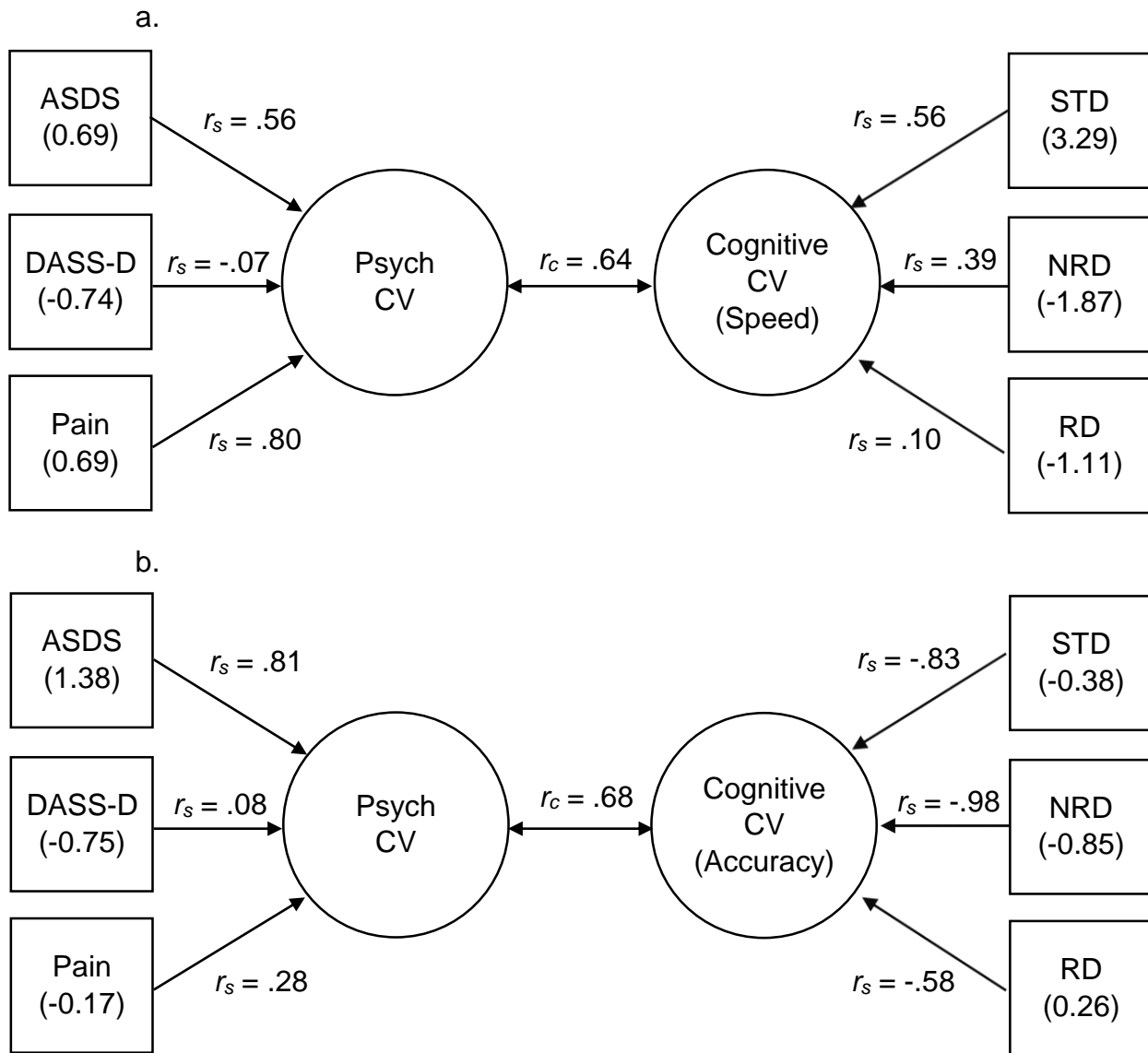
Figure 2. Canonical correlation (r_c), structure (r_s), and standardized function coefficients for psychological variables and extended Ruff 2 & 7 speed (a) and accuracy (b) variables. Standardized function coefficients of each variable are displayed in parentheses within each observed variable box. ASDS = Acute Stress Disorder Scale total; CV = canonical variate; DASS-D = Depression Anxiety and Stress Scale 21-item depression subscale; NRD = non-relevant distraction condition; pain = subjective pain rating; Psych = psychological; r_c = canonical correlation coefficient; RD = relevant distraction condition; r_s = structure coefficient; STD = standard condition.

higher cognitive CV scores. In contrast, higher NRD speed scores were associated with lower cognitive CV scores, although that relationship was not as strong. The RD speed variable appeared to show a suppressor effect. While it showed only a small correlation with the cognitive CV, it did contribute to the prediction of cognitive CV scores according to the standardized function coefficient, likely by reducing redundancy.

To summarize, the positive correlation between the psychological CV and cognitive CV indicated that as psychological CV scores increased (and pain and acute post-traumatic stress increased), cognitive CV scores increased (reflecting higher STD speed scores and possibly lower NRD speed scores). Therefore, greater pain and acute post-traumatic stress were associated with higher speed scores under non-distracting conditions. Scatterplots of the relationships among untransformed ASDS total scores, pain ratings, and speed scores in the STD and NRD conditions confirmed the direction of these relationships (see Figure B1, Appendix B).

Extended Ruff 2 & 7 Accuracy

As shown in Figure 2b, the psychological and the extended Ruff 2 & 7 accuracy CVs shared a large degree of variance (45.78%). Acute post-traumatic stress and depression showed the largest standardized function coefficients while the function coefficient of pain was minimal. The structure coefficients (and squared values) provided further clarification. Acute post-traumatic stress showed the largest correlation with the psychological CV—65.29% of its variance contributed to CV scores—whereas pain shared less variance and depression shared negligible variance with the psychological CV (7.95% and 0.71%, respectively). Together, this pattern suggests that more severe acute post-traumatic stress symptoms were associated with higher psychological CV scores. Overall, pain did not appear to contribute substantially to the canonical function. Depression appeared to suppress redundant information shared with other psychological variables to improve prediction despite its minimal correlation with the psychological CV.

In terms of accuracy, NRD scores showed a larger function coefficient than either STD or RD scores. Structure coefficients were large across all three conditions. Overall, this pattern suggested that higher NRD accuracy scores were associated with lower cognitive CV scores. The strong correlations between the cognitive CV and all accuracy scores, considered in light of the smaller STD and RD function coefficients, suggested that the accuracy variables redundantly shared a significant amount of predictive power, which was eliminated in the distribution of the function coefficients.

To summarize, the positive correlation between the psychological CV and cognitive CV suggested that as psychological CV scores increased (and acute post-traumatic stress increased), cognitive CV scores also increased (and NRD accuracy scores decreased). Therefore, acute post-traumatic stress was associated with lower NRD accuracy scores. Strong correlations between the cognitive CV and accuracy scores in each task condition suggests that the relationship between more severe acute post-traumatic stress symptoms and lower accuracy scores may have applied across different task conditions despite the differential distribution of function coefficients. Scatterplots of the relationships between untransformed ASDS total scores and untransformed accuracy scores in each condition confirmed the direction of these relationships (Figure B2, Appendix B).

Discussion

The current study examined the associations between self-report measures of acute post-traumatic stress, depression, and pain, and cognitive performance on neuropsychological measures of attention, memory, processing speed, reaction time, working memory, and verbal fluency in a consecutive sample of adult trauma patients within the acute to sub-acute period following mTBI. A series of CCAs revealed significant relationships between the psychological variables of acute post-traumatic stress and pain, and performance on the extended version of the Ruff 2 & 7 Selective Attention Test.

It was hypothesized that acute post-traumatic stress, depression, and pain would be associated with lower performance on neuropsychological measures. This hypothesis was only partially supported. The strongest association was observed between acute post-traumatic stress and extended Ruff 2 & 7 accuracy, whereby more severe symptoms of acute post-traumatic stress were associated with lower accuracy scores. The effect size of this association was large, with over half of the variance in ASDS total scores associated with up to 96% of variance in the extended Ruff 2 & 7 accuracy scores. This relationship appeared to hold across all task conditions. Thus, in the acute to sub-acute phase following mTBI, while simultaneously considering the effects of depressive symptoms and pain, more severe acute post-traumatic stress was associated with lower accuracy on an attentional task across varying levels of cognitive demand.

A significant large association was also present between the psychological factors of pain and acute post-traumatic stress, and speed performance on the extended Ruff 2 & 7 task. Unexpectedly, the direction of these relationships suggested that more severe pain and acute post-traumatic stress were associated with higher speed scores under standard non-distracting conditions. In contrast, and consistent with hypotheses, greater pain and acute post-traumatic stress were associated with lower speed scores on the extended Ruff 2 & 7 under conditions of auditory distraction although this relationship was not as strong.

The current results extend Batchelor et al.'s (1995) report that anxiety modulates cognitive performance of mTBI patients by demonstrating that acute post-traumatic stress was linked to both lower and higher scores on an attentional task. Lower accuracy in the current sample is consistent with research demonstrating negative impacts of anxiety on cognitive performance (Castaneda et al., 2008; Derakshan & Eysenck, 2009; Eysenck et al., 2007; Johnsen, & Asbjørnsen, 2008; Salthouse, 2012). The consistency of these accuracy results across task conditions further suggests that individuals with more severe acute post-traumatic

stress following mTBI may experience cognitive difficulties across a range of environmental conditions, not only when attentional demands are particularly high.

Higher speed scores under less demanding conditions amongst mTBI individuals with greater pain and elevated acute post-traumatic stress was not expected on the basis of the existing literature regarding pain and acute post-traumatic stress (Derakshan & Eysenck, 2009; Etherton et al., 2006; Eysenck et al., 2007; D. J. Moore et al., 2013; Salthouse, 2012; Sanchez, 2011), however, other studies have found faster response times in the presence of acute pain (Babiloni et al., 2004; Seminowicz & Davis, 2007). On the other hand, the results of lower speed scores in the presence of more severe pain and acute post-traumatic stress under auditory distraction conditions were consistent with existing literature (Derakshan & Eysenck, 2009; Etherton et al., 2006; Eysenck et al., 2007; D. J. Moore et al., 2013; Salthouse, 2012; Sanchez, 2011).

The current results contrast with previous findings reporting no relationship between pain and cognition in the acute (Landre et al., 2006) and post-acute mTBI period (Jamora et al., 2013; Tsushima & Newbill, 1996). They are, however, somewhat consistent with results obtained by Beaupré et al. (2012) who assessed mTBI patients in the post-acute phase. In their study, pain correlated with both higher and lower scores on different visual selective attention tests from the TEA but pain was not found to be related to performance on the standard Ruff 2 & 7 Selective Attention Test. Methodological differences, including different measures, samples, and intervals between injury and assessment, may explain the discrepancies between these results.

The pattern of speed results across task conditions extends the existing mTBI evidence by suggesting that the associations of pain and acute post-traumatic stress with cognition may depend on the level of cognitive demand. Individuals experiencing more severe pain or acute post-traumatic stress may only demonstrate higher cognitive performance under non-distracting or less demanding conditions (Seminowicz & Davis, 2007) whereas they may

perform at lower levels under more demanding conditions. A possible explanation of the results of higher speed performance may be that pain and anxiety reactions, such as acute post-traumatic stress, are both associated with increased sympathetic nervous system activity and physiological arousal (Bremner, Krystal, Southwick, & Charney, 1996; Chapman & Nakamura, 1999; Felmingham, Rennie, Gordon, & Bryant, 2012; Jänig, 1995), which may facilitate attentional processes (Duschek, Muckenthaler, Werner, & Reyes del Paso, 2009; see also Berntson, Sarter, & Cacioppo, 2006; Coull, 1998) and motor responses (Jänig, 1995; Zwosta, Hommel, Goschke, & Fischer, 2013). Under more demanding conditions, these associations may become less important factors in overall performance. It is also possible that pain and acute post-traumatic stress were associated with speed–accuracy trade-offs which favoured speed under less demanding conditions. Because the speed and accuracy data were analyzed separately, however, this suggestion remains tentative and requires further investigation.

Although the canonical variates derived from cognitive measures such as the CTIP and the Brown–Peterson task also shared a medium to large degree of variance (i.e., 13–25%) with the psychological canonical variates, these associations did not reach significance. Due to the modest sample size, it cannot be concluded that the remaining cognitive variables were unrelated to the psychological variables. Similarly, it cannot be suggested that depression had no association with cognitive functioning in the current sample of trauma patients with mTBI. Finally, acute post-traumatic stress and pain may have other relationships with cognitive functioning that were undetected in the present study.

By using canonical correlation analysis, it was possible to concurrently consider multiple psychological factors and their relative associations with the cognitive variables, however, limitations of the study included a small sample size and reduced statistical power. The lack of a trauma comparison group also prevented conclusions about whether the results are specific to mTBI. Additionally, there remains a possibility that there was some degree of

overlap among the symptoms and constructs measured by the psychological variables (e.g., negative affectivity or arousal; Brown, Chorpita, Korotitsch, & Barlow, 1997; Gross & Collins, 1981; Mounce, Keogh, & Eccleston, 2010; Shackman et al., 2011), as well as between these psychological variables and other sequelae of mTBI (e.g., 'post-concussive' symptoms; Iverson, 2006; Iverson & McCracken, 1997). Thus, despite attempts to control for confounding relationships, it is unlikely that the psychological variables in the current study represent pure constructs. In a similar vein, although the extended Ruff 2 & 7 task appeared to be highly sensitive, the varied demands of this task—requiring selective, divided and sustained attentional skills, processing speed, and psychomotor functions (Cicerone, 1996; Ruff, 1994; Ruff & Allen, 1996)—prevent conclusions about specific cognitive processes. Finally, it is important to note that these findings of association do not allow causal inferences. While it is possible that psychological distress and pain may impact cognitive functioning, an opposite or bidirectional influence is also conceivable. Alternatively, all factors may be related to an unmeasured variable that may explain the observed associations and which may pre-exist the mTBI.

Future research using larger samples is required to replicate these results and further investigate the mechanisms underlying the associations of acute post-traumatic stress, depression, and pain with cognitive functioning following mTBI. Prospective longitudinal designs will be essential to investigate the directions of these relationships. Potential moderators of these relationships, such as opioid intake or psychiatric history, also require further study. In the present study, the cognitive measures showing the strongest associations with psychological factors were tasks that incorporated increasing levels of cognitive demands (i.e., dual-tasks or those which included increasing difficulty or extended durations). This supports previous research suggesting that such tasks may be the most sensitive in detecting differences in and moderators of mTBI outcome (Bernstein, 2002; O'Jile et al., 2006; Stuss et al., 1985). These tasks may also have the greatest ecological validity with

respect to the difficulties that mTBI patients may face as they recover and return to the demands of daily life (Bernstein, 1999; Mateer & Mapou, 1996; Stuss et al., 1985).

The current study provided a broad investigation into the associations between psychological factors and cognitive functioning in the acute to sub-acute phase of mTBI. Large associations of acute post-traumatic stress and pain with cognitive performance emphasize the importance of considering comorbid psychological factors in the assessment of cognitive functioning of adult trauma patients with mTBI in clinical and research settings. Attentional tasks or tasks with increasing cognitive demands may prove the most sensitive to these associations. The results also raise the possibility that the experiences of acute post-traumatic stress and pain may be related in complex ways to the cognitive performance of hospitalized individuals recovering from mTBI. The management of patients in the acute to subacute stage of mTBI recovery should involve the assessment of cognitive and psychological functioning. Psychological factors should be considered in the interpretation of neuropsychological test results. Interventions that address both cognitive and psychological factors may be the most successful in optimizing recovery from mTBI.

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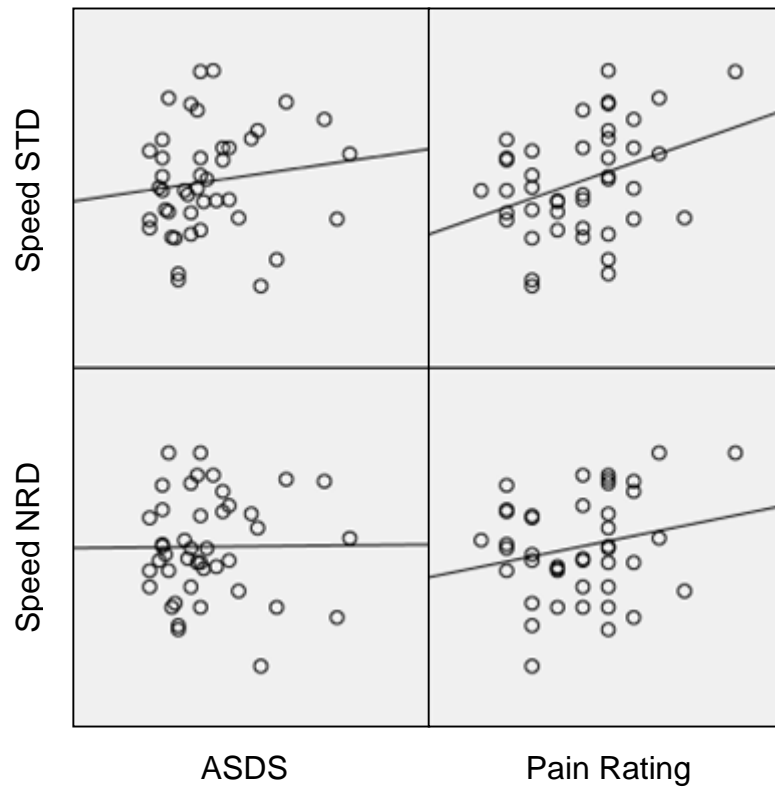
Appendix B

Figure B1. Scatterplots of the relationships between the untransformed variables of Acute Stress Disorder Scale (ASDS) total scores, subjective pain ratings, and extended Ruff 2 & 7 speed scores under standard (STD) and non-relevant distraction (NRD) conditions.
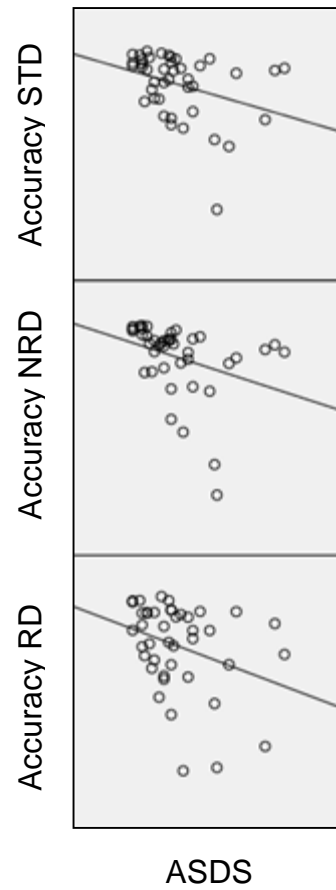
Figure B2. Scatterplots of the relationships between untransformed Acute Stress Disorder

Scale (ASDS) total scores and untransformed extended Ruff 2 & 7 accuracy scores under

standard (STD), non-relevant distraction (NRD), and relevant distraction (RD) conditions.

Chapter 4

Acute post-traumatic stress, depression, and pain following mild traumatic brain injury:

Contrasting associations with attentional performance under increasing cognitive

demands.

Abstract

The effect of psychological distress and pain on cognitive outcome following mild traumatic brain injury (mTBI) has received little attention despite the prevalence and comorbidity of these symptoms. The first aim of the current study was to investigate whether acute post-traumatic stress, depression, and pain were associated with speed and accuracy performance on an attentional test in individuals following mTBI. The second aim was to explore whether these associations differed as cognitive demands increased. Consecutive adult mTBI admissions to a Level 1 trauma hospital were screened for inclusion. Forty-two participants completed self-report measures of acute post-traumatic stress, depression, and pain, and were assessed on the extended Ruff 2 & 7 task under standard, non-relevant distraction, and relevant distraction conditions an average 2.86 ($SD = 2.26$) days post-injury. Repeated measures multivariate analyses of variance revealed that more severe acute post-traumatic stress was associated with lower accuracy scores whereas more severe depression was associated with higher accuracy scores. More severe acute post-traumatic stress and greater pain were associated with larger declines in speed scores as cognitive demands increased while more severe depression was associated with smaller declines in speed scores. Greater severity of depressive symptoms was associated with lower subjective ratings of mental effort while performing the task whereas greater pain was associated with higher subjective ratings of mental effort. Acute post-traumatic stress, depression, and pain showed distinct and contrasting associations with attentional performance in adult trauma patients in the acute to sub-acute phase following mTBI. The findings highlight the need to consider comorbid psychological distress and pain when interpreting the neuropsychological test scores of mTBI patients in clinical and research settings.

Acute Post-Traumatic Stress, Depression, and Pain following Mild Traumatic Brain Injury: Contrasting Associations with Attentional Performance under Increasing Cognitive Demands.

The acute to sub-acute cognitive sequelae of mild traumatic brain injury (mTBI) are well recognized (Belanger, Curtiss, Demery, Lebowitz, & Vanderploeg, 2005; Carroll, Cassidy, Peloso, et al., 2004; Frencham, Fox, & Maybery, 2005; Rohling et al., 2011; Schretlen & Shapiro, 2003). Mild deficits that typically resolve within one to three months post-injury are observed in the domains of attention, processing speed, memory, and executive functioning (Belanger et al., 2005; Binder, Rohling, & Larrabee, 1997; Frencham et al., 2005; Rohling et al., 2011; Schretlen & Shapiro, 2003). Psychological symptoms are also common in the acute to sub-acute recovery period (defined as the period up to 30 days post-injury; McCrea et al., 2009; Bazarian et al., 1999). Frequently reported symptoms include post-traumatic stress (Broomhall et al., 2009; Harvey & Bryant, 1998; Levin et al., 2013; Meares et al., 2006; Meares, Shores, Taylor, Batchelor, et al., 2011) and depression (Federoff et al., 1992; Meares et al., 2006). Various forms of psychological distress often present comorbidly (Bryant et al., 2010; Feinstein, Hershkop, Jardine, & Ouchterlony, 2000; Harvey & Bryant, 1998; Jorge et al., 2004), highlighting the need for researchers and clinicians to consider a range of symptoms simultaneously.

Literature from the field of psychiatry has illustrated effects of anxiety (Castaneda, Tuulio–Henriksson, Marttunen, Suvisaari, & Lönnqvist, 2008; Henry, 2006; Johnsen & Asbjørnsen, 2008) and depressive disorders (Castaneda et al., 2008; Lee, Hermens, Porter, & Redoblado–Hodge, 2012) on various cognitive domains including attention, processing speed, learning, memory, and executive functioning. Similarly, research on subclinical mood symptoms and induced mood states in non-clinical samples has indicated reductions in attentional skills, processing speed, and executive functions, as well as broad cognitive constructs such as general intelligence (Derakshan & Eysenck, 2009; Eysenck, Derakshan,

Santos, & Calvo, 2007; Salthouse, 2012; Seibert & Ellis, 1991). Such results have led

researchers to propose that psychological distress consumes cognitive resources (Andrews &

Thomson, 2009; Beck, 1985; Ellis & Ashbrook, 1988; Eysenck et al., 2007; Pessoa, 2009, see

also Erber & Tesser, 1992; Kron, Schul, Cohen, & Hassin, 2010; Van Dillen & Koole, 2007).

Because cognitive resources are assumed to be limited in their capacity (Baddeley, 2003;

Kahneman, 1973; Moray, 1967; Norman & Bobrow, 1975), distress can lead to difficulties in

performing cognitive tasks (Ellis & Ashbrook, 1988; Eysenck et al., 2007; Seibert & Ellis,

1991). A corollary of this proposal is that psychological distress is more likely to

compromise performance on more complex cognitive tasks that require the full capacity of

resources (Ellis & Ashbrook, 1988; Eysenck et al., 2007).

Despite the prevalence of psychological symptoms following mTBI, as well as

longstanding calls to address this potentially complicating factor (Alexander, 1995; Carroll,

Cassidy, Peloso, et al., 2004; Dikmen & Levin, 1993), few studies have examined whether

psychological distress affects cognitive outcome following mTBI (Carroll, Cassidy, Peloso, et

al., 2004; E. L. Moore, Terryberry–Spohr, & Hope, 2006), particularly in the acute to sub-

acute recovery phase. Two studies that have addressed this question (Batchelor, Harvey, &

Bryant, 1995; Preece & Geffen, 2007) have indicated associations of anxiety (Batchelor et al.,

1995) and pre-existing depression (Preece & Geffen, 2007) with cognitive functioning. The

generalizability of these results is limited, however, by the use of a non-consecutive series

(Batchelor et al., 1995) and case–control design (Preece & Geffen, 2007).

Pain is also a common complaint following mTBI (Alves, Macchiocchi, & Barth,

1993; Bazarian et al., 1999; Faux, Sheedy, Delaney, & Riopelle, 2011; Landre, Poppe, Davis,

Schmaus, & Hobbs, 2006; Meares et al., 2006; Ponsford, Cameron, Fitzgerald, Grant, &

Mikocka–Walus, 2011). Pain is frequently reported in conjunction with psychological

symptoms in a range of populations (Gerhardt et al., 2011; Linton, 2000; L. J. Williams,

Pasco, Jacka, Dodd, & Berk, 2012), including mTBI (Jamora, Schroeder, & Ruff, 2013).

Although the neuropsychological impact of pain is not clearly understood, experimental studies of laboratory-induced acute pain and clinical studies of chronic pain have generally suggested negative effects on cognition, including attention and processing speed (Hart, Martelli, & Zasler, 2000; D. J. Moore, Keogh, & Eccleston, 2013; Moriarty, McGuire, & Finn, 2011; Nicholson, 2000). Such findings have also prompted the proposition that pain consumes cognitive resources, leading to detrimental effects on cognition, particularly attention (Eccleston & Crombez, 1999; Grigsby, Rosenberg, & Busenbark, 1995; Legrain et al., 2009; Sanchez, 2011). Most studies, however, have focused on experimentally induced pain or chronic pain, each of which differ in important ways (e.g., in duration, degree of associated distress, and pathophysiology) from acute real-world pain (Cervero & Laird, 1996; Edens & Gil, 1995; Gagliese, 2007; D. J. Moore, Keogh, Crombez, & Eccleston, 2013; Nicholson, 2000).

Few studies have examined the effect of pain on cognitive functioning following mTBI (Beaupré, De Guise, & McKerral, 2012; Jamora et al., 2013; Tsushima & Newbill, 1996). While two studies detected no significant association between pain and cognitive performance (Jamora et al., 2013; Tsushima & Newbill, 1996), Beaupré et al. (2012) found mixed associations between pain and attentional performance. However, as none of the studies recruited consecutive trauma presentations, the representativeness of their samples is questionable. Additionally, no study controlled for the effect of comorbid distress. Thus, the evidence regarding the association between pain and cognitive functioning after mTBI remains limited.

To the best of the authors' knowledge, no study has concurrently examined the effects of psychological distress and pain on cognitive functioning in the acute to sub-acute phase following mTBI. The first aim of the present study was to examine whether acute post-traumatic stress, depression, and pain were associated with cognitive performance on an attentional task—an extended version (Cicerone, 1996) of the Ruff 2 & 7 Selective Attention

Test (Ruff & Allen, 1996)—in the acute to sub-acute period following mTBI in adult trauma patients. Attentional tasks are sensitive to the acute cognitive effects of mTBI (Belanger et al., 2005; Frencham et al., 2005; Rohling et al., 2011), even when controlling for the effects of traumatic injury (Levin et al., 2013; Peterson, Stull, Collins, & Wang, 2009). It was hypothesized that acute post-traumatic stress, depression, and pain would be associated with lower scores on the speed and accuracy measures of the extended Ruff 2 & 7 task.

Tasks that incorporate increasing levels of cognitive demand, including dual-tasks, may be particularly sensitive to subtle cognitive dysfunction after mTBI (Cicerone, 1996; Paré, Rabin, Fogel, & Pépin, 2009; Stuss et al., 1985), including when participants are tested several years after their injury (Bernstein, 2002; Blanchet, Paradis–Giroux, Pépin, & McKerral, 2009; Segalowitz, Bernstein, & Lawson, 2001). Consequently, the second aim was to examine whether the associations of acute post-traumatic stress, depression, and pain with cognitive performance on the extended Ruff 2 & 7 task (Cicerone, 1996) differed as cognitive demands increased. Based on theory and previous research (Derakshan & Eysenck, 2009; Eccleston & Crombez, 1999; Ellis & Ashbrook, 1988; Eysenck et al., 2007; Legrain et al., 2009; Sanchez, 2011), it was hypothesized that acute post-traumatic stress, depression, and pain would be associated with larger declines in speed and accuracy scores as cognitive demands increased. The association between these factors and subjective ratings of mental effort expended during the task was also assessed. It was expected that participants with psychological distress and pain would subjectively report elevated mental effort during the task. Additionally, the influence of self-reported psychiatric history and recent opioid intake on the results was explored due to possible links between these factors and psychological and cognitive outcomes following mTBI (Fann et al., 2004; Meares et al., 2006; 2008; Meares, Shores, Taylor, Batchelor, et al., 2011; Ponsford et al., 2012). It was anticipated that self-reported psychiatric history may be associated with the relationship between psychological

distress and cognitive performance while recent opioid intake (within the preceding 24 hours)

may be associated with the relationship between pain and cognitive performance.

Method

Sample

Consecutive trauma admissions to a Level 1 trauma hospital were screened for

inclusion over the period from April 2011 to July 2012. The current sample of mTBI patients

was recruited as part of a larger study that included complicated mTBI and moderate TBI

patients. In the current study, only participants with uncomplicated mTBI were included

(Kashluba, Hanks, Casey, & Millis, 2008; D. H. Williams, Levin, & Eisenberg, 1990).

Patients were eligible to participate if they had sustained a mTBI according to World Health

Organization (WHO) diagnostic criteria (Carroll, Cassidy, Holm, Kraus, & Coronado, 2004)

that includes (i) a duration of post-traumatic amnesia (PTA) of less than 24 hours, (ii) a

Glasgow Coma Scale (GCS) score of 13 to 15 within 30 minutes of injury or upon

presentation for healthcare, and (iii) a loss of consciousness (LOC) for no longer than 30

minutes. Additional inclusion criteria included being (a) aged between 18 and 65 years, (b)

admitted to hospital within 24 hours of injury, (c) able to complete the assessment within 14

days of injury, and (d) sufficient English language comprehension and fluency to enable valid

test administration. Exclusion criteria included (a) acute intracranial pathology or depressed

skull fracture on neuroimaging (Kashluba et al., 2008; D. H. Williams et al., 1990), (b) pre-

existing cognitive impairment, (c) an IQ of less than 70, (d) psychotic illness, (e) physical

injury as a result of self-harm, (f) suicidality, (g) medically unable to participate (i.e., physical

injuries prevented the participant from undertaking the assessment), (h) being the subject of

forensic investigation, (i) being an interstate or overseas visitor (to ensure availability for

planned follow-up assessments), (j) being pregnant (to avoid possible confounds with

pregnancy-related cognitive deficits; De Groot, Vuurman, Hornstra, & Jolles, 2006), or (k)

suboptimal effort on the embedded measures from the California Verbal Learning Test, 2nd

ed. (CVLT-II; Delis, Kaplan, Kramer, & Ober, 2000) and the Computerized Test of Information Processing (CTIP; Tombaugh & Rees, 2008). Suboptimal effort was defined as performance at or below cut-off on the sum of learning trials and long delay cued recall trial on the CVLT-II (Millis, Putnam, Adams, & Ricker, 1995). Suboptimal performance on the CTIP was required to meet multiple criteria as specified by Tombaugh and Rees (2008; Willison & Tombaugh, 2006). Participants were excluded if they demonstrated suboptimal performance on both embedded effort measures (Heilbronner et al., 2009; Larrabee, 2008; Slick, Sherman, & Iverson, 1999; Victor, Boone, Serpa, Buehler, & Ziegler, 2009).

The flow of admissions through the screening, recruitment, and assessment process is illustrated in Figure 1. Ninety-eight participants met criteria for inclusion and were invited to participate. Forty-one patients (41.8%) refused.

Measures

Participants completed the Acute Stress Disorder Scale (ASDS; Bryant, Moulds, & Guthrie, 2000), a reliable and valid 19-item self-report measure that is based on criteria from the *Diagnostic and Statistical Manual of Mental Disorders* (*DSM*; 4th ed.; American Psychiatric Association [APA], 1994). The total score was analyzed and consisted of the sum of all items with the exception of the amnesia item. This item was excluded as patients' experience of PTA, psychogenic amnesia, or opioid analgesia may have confounded their responses (Bryant & Harvey, 1999; O'Donnell, Creamer, Bryant, Schnyder, & Shalev, 2003). The total score was used in favor of subscale scores that reflect symptom clusters in order to preserve statistical power. This approach also aligns with the recent revision of the *DSM* (5th ed., APA, 2013) in which the diagnosis of acute stress disorder is based on the overall symptom severity rather than criteria regarding specific symptom clusters (APA, 1994).

Depressive symptomatology was measured using the 21-item version of the Depression Anxiety Stress Scale (DASS-21; Lovibond & Lovibond, 1995). The DASS-21 depression subscale is a reliable and valid measure of depressive symptoms (Antony, Bieling,
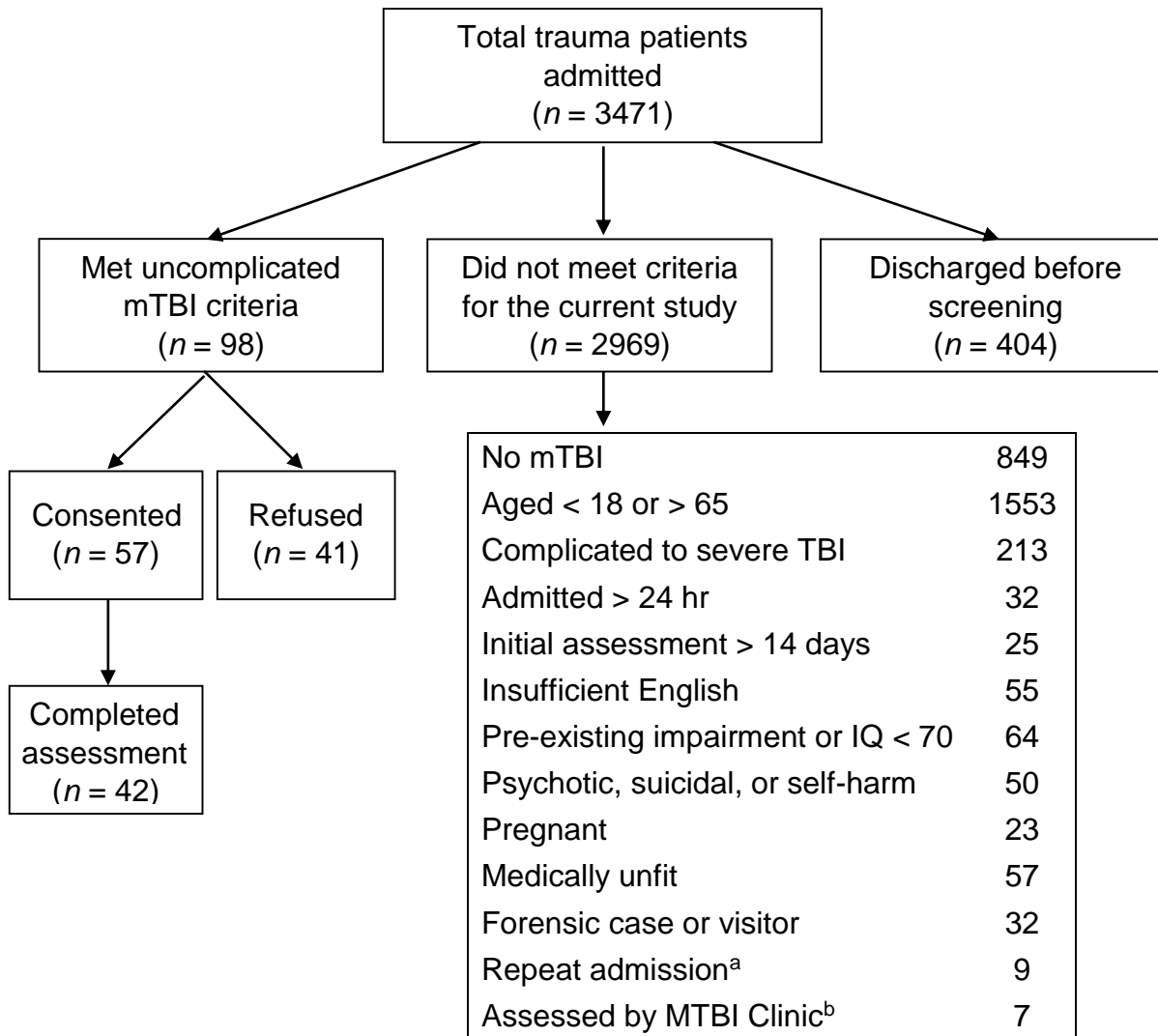
Figure 1. Flow of trauma admissions through the screening, recruitment, and assessment

process. mTBI = mild traumatic brain injury; TBI = traumatic brain injury. [a]Patients were

excluded if they were re-admitted for the same injury and had already undergone study

screening. [b]Patients were excluded if they had already undergone a neuropsychological

assessment within the hospital's MTBI Clinic to avoid possible practice effects on cognitive

tasks.

Cox, Enns, & Swinson, 1998; Henry & Crawford, 2005; Lovibond & Lovibond, 1995; Ng et al., 2007) in TBI samples (Dahm, Wong, & Ponsford, 2013) and excludes somatic symptoms which may be confounded by patients' physical injuries. The sum of the depression subscale (DASS-D) was used to assess symptom severity (Lovibond & Lovibond, 1995).

Continuous measures of the severity of acute post-traumatic stress and depressive symptoms were utilized instead of categorical diagnostic variables in order to preserve sensitivity and statistical power. Some researchers have argued that dimensional measures of symptom severity may more accurately reflect the continuum of psychopathology that underlie responses to these measures (A. M. Ruscio & Ruscio, 2002; A. M. Ruscio, Ruscio, & Keane, 2002; J. Ruscio & Ruscio, 2000; Slade & Andrews, 2005) including those experienced after mTBI (E. L. Moore et al., 2006) and trauma (Bryant, Friedman, Speigel, Ursano, & Strain, 2011; A. M. Ruscio et al., 2002).

A subjective rating of current pain intensity was obtained by asking participants to rate their pain on an 11-point numerical rating scale ranging from 0 (*no pain*) to 10 (*pain as bad as it could be*; Jensen & Karoly, 2011). Numerical rating scales have evidence for reliability and validity in measuring pain (Good et al., 2001; Hjermstad et al., 2011; Jensen & Karoly, 2011).

As a part of a larger neuropsychological battery, participants completed an extended version of the Ruff 2&7 Selective Attention Test (Ruff & Allen, 1996) as described by Cicerone (1996). The procedure was replicated according to the information provided by Cicerone (1996). The original Ruff 2 & 7 Selective Attention Test measures selective and sustained attention (Ruff & Allen, 1996). Individuals are asked to mark targets (the numbers 2 and 7) which are randomly interspersed with other digits or letters as quickly as possible within a specified time limit. In the extended version of the test, participants completed 10 trials under *standard* (STD) conditions, 10 trials under a *non-relevant distraction* (NRD) of a radio playing in the background, 10 trials under a *relevant distraction* (RD) condition,

followed by another 10 trials under STD conditions. The RD consisted of a dual-task in which participants marked targets in addition to answering simple arithmetic problems (addition, subtraction, multiplication, and division) presented every 5 seconds via an audio recording. The RD condition has been posited to require the ability to shift attention and actively coordinate attentional resources (Cicerone, 1996). Each condition yielded two scores. The speed score consisted of the number of correctly marked targets, and the accuracy score was the percentage of responses that were correct hits. In the RD condition, the number of arithmetic errors was subtracted from total correct hits prior to calculating speed and accuracy scores (Cicerone, 1996). Raw scores were used for all calculations. Participants also completed the Test of Premorbid Functioning (TOPF), a valid and reliable reading measure used to estimate premorbid intellectual functioning (Holdnack & Drozdick, 2009). A similar measure has shown evidence of validity in TBI (Green et al., 2008).

In addition to these performance measures, participants completed a subjective rating of mental effort (Paas, 1992) widely used in instructional research paradigms (Paas, Tuovinen, Tabbers, & Van Gerven, 2003). At the completion of the extended Ruff 2 & 7, participants were asked to rate how much mental effort they were required to invest during each condition on a 10-point scale ranging from 1 (*very, very low mental effort*) to 9 (*very, very high mental effort*).

Procedures

Ethical approval was obtained from the Western Sydney Local Health Network and Macquarie University Human Research Ethics Committees. Eligible patients were identified from weekday lists that included weekend trauma admissions. All patients were screened, and medical records reviewed, to evaluate eligibility according to the inclusion and exclusion criteria. If eligible, they were invited to participate. All participants provided informed written consent. Participants were cleared from PTA by hospital staff using the Abbreviated

Westmead PTA Scale (Meares, Shores, Taylor, Lammél, & Batchelor, 2011) or the

Westmead PTA Scale (Shores, Marosszeky, Sandanam, & Batchelor, 1986).

Demographic information was collected using a structured interview. Not all

participants were administered a PTA scale upon presentation to the emergency department.

Consequently, an estimate of PTA duration was obtained retrospectively by asking

participants to describe their memories following their injury using open-ended questions

such as "What is the first thing you remember after the injury?" followed by "And what

happened then?" (Gronwall & Wrightson, 1980; Levin, O'Donnell, & Grossman, 1979).

Objective information of acute clinical indicators such as LOC, GCS scores, confusion, and

disorientation were obtained from ambulance and medical records. Information regarding

other physical injuries was classified into orthopedic (e.g., fractures, dislocations), soft tissue

(e.g., significant lacerations, abrasions, hematomas), internal, or other (e.g., subconjunctival

hemorrhage) categories (adapted from Landre et al., 2006). Opioid (morphine, codeine,

oxycodone, oxycodone hydrochloride, tramadol hydrochloride, fentanyl and methadone)

intake in the 24 hours prior to assessment was recorded as present or absent. Self-reported

psychiatric history was recorded as present if participants reported seeing a psychiatrist,

psychologist, or counsellor for mental health issues in the past or if they reported ever being

prescribed medication to treat their mood. Assessments were conducted by four provisional

psychologists undertaking postgraduate training in clinical neuropsychology. To avoid

effects of order or fatigue, participants were randomized to complete psychological measures

then cognitive measures or vice versa (Urbaniak & Plous, 2011).

Statistical Analysis

Patients who consented and refused were compared to evaluate any differences in

demographic or injury variables using independent sample *t*-tests and chi-square tests, or

Mann–Whitney *U*-tests for non-normally distributed variables. Participants with and without

missing data were compared using independent sample *t*-tests, chi-square tests, and Mann–

Whitney *U*-tests to determine if the subgroup with missing data differed from those with complete data. The speed and accuracy scores obtained during the early and late trials of the STD condition were compared using paired sample *t*-tests to determine whether there were differences in performance before they were summed into one STD speed score and one STD accuracy score (Cicerone, 1996). The assumptions of independent observations and normality were met with the following exceptions. Accuracy scores were negatively skewed and were reflected and normalized using a logarithmic transformation (Tabachnick & Fidell, 2013). ASDS total scores and DASS-D scores were transformed using inverse and logarithmic transformations, respectively, because both were positively skewed (Tabachnick & Fidell, 2013). Cognitive and psychological variables were reversed as necessary so higher scores on all cognitive variables reflected better performance and higher scores on all psychological variables indicated more severe symptomatology.

The data were analyzed using three repeated measures multivariate analyses of variance (MANOVAs). Speed scores, accuracy scores, and mental effort ratings were the dependent variables. In each analysis, scores or ratings obtained under the STD, NRD, and RD conditions formed a three-level within-subjects factor. The ASDS total score, DASS-D score, subjective pain rating, and TOPF standard score were included as numeric between-subjects independent variables in each analysis. TOPF standard score was included to control for premorbid intellectual ability and because it was significantly correlated with transformed RD accuracy scores ($r = .44$, $p = .003$) as well as transformed ASDS total scores ($r = -.42$, $p = .005$). To further investigate interaction effects, planned interaction contrasts were used to evaluate the associations of acute post-traumatic stress, depression, and pain with the difference between the means in the STD and NRD conditions, NRD and RD conditions, and STD and RD conditions. Due to the exploratory nature of the study, an alpha level at .05 was retained for all tests of significance to minimize Type II errors. To verify that the order of test administration did not have a significant effect on the results, test order was included as an

independent variable in a separate analysis. Bivariate Pearson correlations were calculated to assess the relationships between ASDS total scores, DASS-D scores, and subjective pain ratings.

To evaluate whether the results were influenced by self-reported psychiatric history, the main MANOVAs examining speed scores, accuracy scores, and mental effort ratings were repeated including self-reported psychiatric history as an independent variable. Because opioids are frequently used as analgesics in trauma settings and may also affect cognitive performance (Meares et al., 2006; Zacny, 1995), the impact on the results of opioid intake in the 24 hours preceding the assessment was examined. Bivariate Pearson correlations were calculated between opioid intake and the following variables: pain ratings, speed scores, accuracy scores, and mental effort ratings. Additionally, the three main MANOVAs were repeated including the dichotomous opioid intake variable. Partial eta squared (η_p^2) values were interpreted. These values reflect the degree of variance attributable to the independent variable with the effects of other independent variables removed (Richardson, 2011). Cohen's (1988) classification of effect sizes were used to aid interpretation, whereby partial eta squared values of .01, .06, and .14 correspond to small, medium, and large effects, respectively (Richardson, 2011).

Results

Table 1 provides descriptive statistics of those who consented and refused. There were no significant differences between those who consented and refused in terms of age, $t(94) = -0.70$, $p = .49$, 95% CI [-6.89, 3.31]; gender, $\chi^2(1, 98) < 0.01$, $p = .98$, $\Phi < -.01$; days of hospitalization, Mann–Whitney $U = 1065$, $z = -0.75$, $p = .45$; orthopedic injuries, $\chi^2(1, 97) = 0.55$, $p = .46$, $\Phi = -.08$; soft tissue injuries, $\chi^2(1, 97) < 0.01$, $p = .94$, $\Phi < .01$; internal injuries, $\chi^2(1, 97) = 1.12$, $p = .29$, $\Phi = -.11$; or other injuries, $\chi^2(1, 97) = 1.63$, $p = .20$, $\Phi = .13$. No participant met criteria for suboptimal effort on the embedded effort measures (Millis et al., 1995; Willison & Tombaugh, 2006).

Table 1

Descriptive Statistics of Patients who Participated versus Refused

Variable	Participants (*n* = 57)		Refusers (*n* = 41)	
	M (*SD*)	*n* (%)	*M* (*SD*)	*n* (%)
Age	37.2 (13.8)		35.4 (11.6)	
Days of hospitalization	6.2 (0.8)		6.9 (1.0)	
Male		46 (80.7)		33 (80.5)
Orthopedic injuries		43 (75.4)		34 (82.9)
Soft tissue injuries		25 (43.9)		18 (43.9)
Internal injuries		10 (17.5)		11 (26.8)
Other injuries		7 (12.3)		2 (4.9)

Of the 57 participants, 15 had missing data. Eight did not complete the extended Ruff 2 & 7 task because it was introduced after commencement of the study, three had physical injuries, and one had missing data on the arithmetic component of the extended Ruff 2 & 7 task. Three participants were discharged prior to completing the assessment. Comparisons revealed no significant differences between those with and without missing data in terms of age, $t(55) = .22$, $p = .82$, 95% CI [-7.44, 9.32]; education, $t(55) = 1.24$, $p = .22$, 95% CI [-0.54, 2.30]; TOPF standard score, $t(48) = 1.14$, $p = .26$, 95% CI [-4.19, 15.05]; gender, $\chi^2(1, 57) = 0.01$, $p = .94$, $\Phi = .01$; days of hospitalization, Mann–Whitney $U = 282$, $z = -0.60$, $p = .55$; orthopedic injuries, $\chi^2(1, 56) = 0.12$, $p = .73$, $\Phi = .05$; soft tissue injuries, $\chi^2(1, 56) = 0.18$, $p = .67$, $\Phi = -.06$; internal injuries, $\chi^2(1, 56) = 0.06$, $p = .80$, $\Phi = .03$; or other injuries, $\chi^2(1, 56) = 3.76$, $p = .053$, $\Phi = .26$. There were also no significant differences in terms of ASDS total scores, $t(55) = 0.08$, $p = .94$, 95% CI [-9.02, 9.72]; DASS-D scores, $t(55) = 0.16$, $p = .87$, 95% CI [-5.47, 6.42]; or subjective pain levels, $t(55) = -0.49$, $p = .63$, 95% CI [-1.59, 0.97]. These results suggested this sample was representative of the larger group of 57 participants. The remaining analyses were conducted on 42 participants.

Participants had a mean age of 37.40 ($SD = 14.01$) years and the majority were male (81%). Over half were born in Australia (59.5%) and most spoke English as their first language (78.6%). Participants had a mean of 12.21 ($SD = 2.56$) years of education and the majority were employed (81%). The mean TOPF standard score was 95.31 ($SD = 12.50$). The most common injury mechanism was involvement in a motor vehicle accident (54.8%), followed by falls (23.8%), and cycling accidents (14.3%). Participants were hospitalized for a median of 4 days (range: 1–26) and were assessed a mean of 2.86 ($SD = 2.26$) days post-injury. Of the 42 participants, 23 (54.8%) reported a previous psychiatric history. Thirty-four (81%) participants had been administered at least one opioid analgesic in the 24 hours prior to assessment. Ten participants (23.8%) had more than one type of opioid.

The majority of participants ($n = 27$; 64.3%) had a GCS score of 15 upon presentation while 11 participants (26.2%) had a score of 14 and two (4.8%) had a score of 13. Two participants did not have GCS scores recorded. PTA duration was estimated to be less than 5 minutes in 13 participants (31%), 6 to 60 minutes in eight (19.1%), 61 minutes to 12 hours in 15 (35.7%), and 12 to 24 hours in six participants (14.3%). Thirty-seven participants (88.1%) underwent computed tomography brain scans, all of which were reported as normal. Orthopedic injuries were classified as present in 31 participants (73.8%), soft tissue injuries in 19 (45.2%), internal injuries in seven (16.7%), and other injuries in three participants (7.1%).

Mean raw and transformed scores on the psychological and cognitive measures are provided in Table 2. ASDS total scores were significantly correlated with both DASS-D scores, $r = .64$, $p < .001$, and pain ratings, $r = .50$, $p = .001$. DASS-D scores were also significantly correlated with pain ratings, $r = .31$, $p = .043$. Table 3 shows the proportion of patients reporting clinically significant acute post-traumatic stress symptoms on the ASDS. Clinically significant symptoms were those rated at a medium or higher level. Dissociative and arousal symptoms were the most commonly reported.

Comparison between the early and late STD condition trials of the extended Ruff 2 & 7 task revealed no significant difference in speed scores, $t(41) = -1.83$, $p = .08$, 95% CI [-14.95, 0.76], or accuracy scores, $t(41) = 1.60$, $p = .12$, 95% CI [-0.28, 2.43]. Thus, speed scores for the early and late STD condition trials and accuracy scores for the early and late STD condition trials were combined. The NRD and RD scores were doubled for comparability (Cicerone, 1996). MANOVAs verified no significant main or interaction effects of test order on speed, accuracy, or mental effort. There were no notable changes in the significance or magnitude of the effects of other variables with one exception: The interaction between depression and increasing demand on speed was rendered non-significant, $F(2, 35) = 2.57$, $p = .091$, and decreased slightly in magnitude, $\eta_p^2 = .13$.

Table 2

Raw and Transformed Mean Scores on Psychological and Cognitive Measures

Measure	M^{a}	SD	M tfd	SD tfd
ASDS total[b]	36.62	15.61	-0.032	0.012
DASS-D subscale[c]	6.48	9.57	0.559	0.537
Subjective pain rating	3.86	2.19		
Ext Ruff 2 & 7 Speed STD	229.74	53.60		
Ext Ruff 2 & 7 Speed NRD	227.57	50.99		
Ext Ruff 2 & 7 Speed RD	164.90	54.08		
Ext Ruff 2 & 7 Accuracy STD[d]	92.20	6.73	-0.754	0.360
Ext Ruff 2 & 7 Accuracy NRD[d]	92.57	7.64	-0.710	0.387
Ext Ruff 2 & 7 Accuracy RD[d]	87.18	11.50	-0.987	0.395
Mental effort - STD	4.37	1.70		
Mental effort - NRD	5.11	1.72		
Mental effort - RD	7.05	1.47		

Note. ASDS = Acute Stress Disorder Scale; DASS-D = Depression Anxiety Stress Scale 21-item depression subscale; Ext Ruff 2 & 7 = extended version of the Ruff 2 & 7 Selective Attention Test; NRD = non-relevant distraction condition; RD = relevant distraction condition; STD = standard condition; tfd = transformed.

[a]n = 42. [b]Transformed using inverse function. [c]Transformed using logarithmic function. [d]Reflected and transformed using logarithmic function (Tabachnick & Fidell, 2013).

Table 3

Percentage of Participants Reporting Acute Post-Traumatic Stress Symptoms on the Acute Stress Disorder Scale (ASDS)

ASDS Item	Cluster	%
Difficulty sleeping	Ar	54.8
Feeling in a daze	D	52.4
Amnesic of trauma	D	52.4
Things seeming unreal	D	50.0
Intrusive memories	R	45.2
Feeling outside self	D	35.7
Emotional numbness	D	31.0
Avoiding thoughts of trauma	Av	31.0
Difficulty concentrating	Ar	31.0
Avoiding emotions of trauma	Av	28.6
Feeling irritable	Ar	28.6
Feeling more alert to danger	Ar	28.6
Avoiding talking about trauma	Av	26.2
Distress on trauma reminders	R	16.7
Physiological reactivity	Ar	14.3
Nightmares	R	11.9
Sense of re-experiencing	R	11.9
Feeling jumpy since trauma	Ar	9.5
Avoiding reminders of trauma	Av	4.8

Note. Ar = arousal; Av = avoidance; D = dissociative; R= re-experiencing.

Speed

Figure 2 displays the estimated marginal means of extended Ruff 2 & 7 speed scores derived from the repeated measures MANOVA at the ASDS total mean as well as at one standard deviation above and one standard deviation below, with DASS-D scores, pain ratings, and TOPF standard scores held constant. The figure also shows speed scores at the mean (and one standard deviation above and below) of DASS-D scores, and subjective pain ratings, holding constant all other independent variables. MANOVA results indicated no significant main effects of acute post-traumatic stress, $F(1, 37) = 0.20$, $p = .66$, $\eta_p^2 < .01$, depression, $F(1, 37) = 2.01$, $p = .17$, $\eta_p^2 = .05$, or pain, $F(1, 37) = 2.62$, $p = .11$, $\eta_p^2 = .07$, on speed scores. Speed scores showed significant interactions of large magnitudes between increasing cognitive demands and acute post-traumatic stress, $F(2, 36) = 4.40$, $p = .020$, $\eta_p^2 = .20$; depression, $F(2, 36) = 4.28$, $p = .022$, $\eta_p^2 = .19$; and pain, $F(2, 36) = 6.23$, $p = .005$, $\eta_p^2 = .26$. Planned interaction contrasts revealed that greater acute post-traumatic stress was associated with a larger decline in speed scores from STD to RD conditions, $F(1, 37) = 5.57$, $p = .024$, $\eta_p^2 = .13$, but not from STD to NRD, $F(1, 37) = 2.17$, $p = .15$, $\eta_p^2 = .06$, or NRD to RD, $F(1, 37) = 1.65$, $p = .21$, $\eta_p^2 = .04$. More severe depressive symptoms were associated with a smaller decline in speed scores from STD to RD conditions, $F(1, 37) = 4.43$, $p = .042$, $\eta_p^2 = .11$, but not from STD to NRD, $F(1, 37) = 3.02$, $p = .091$, $\eta_p^2 = .08$, or NRD to RD, $F(1, 37) = 0.91$, $p = .35$, $\eta_p^2 = .02$. Greater pain was associated with significantly larger declines in speed scores from STD to RD, $F(1, 37) = 4.16$, $p = .049$, $\eta_p^2 = .10$, and from STD to NRD conditions, $F(1, 37) = 6.70$, $p = .014$, $\eta_p^2 = .15$, but not from NRD to RD, $F(1, 37) = 0.27$, $p = .61$, $\eta_p^2 < .01$. Scatterplots of the untransformed data confirmed the direction of these relationships (Figure C1, Appendix C).
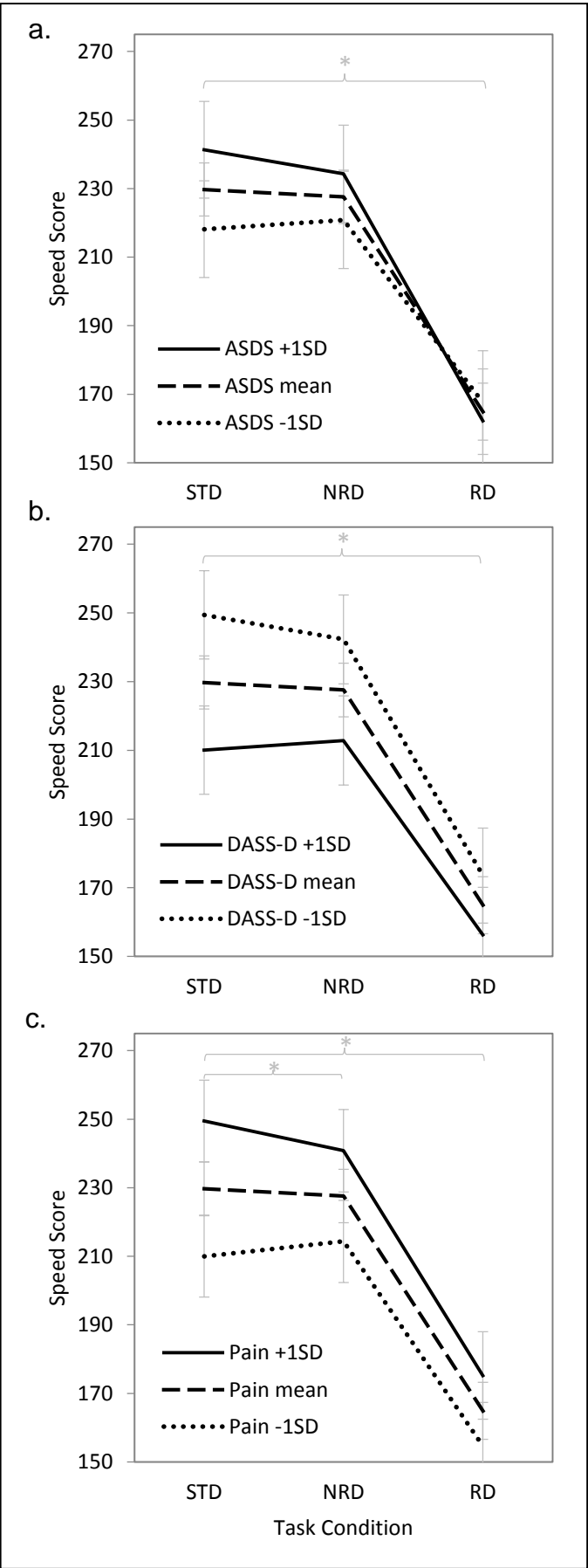
Figure 2. Extended Ruff 2 & 7 speed scores in each task condition at mean levels (and one standard deviation above and below the mean) of acute post-traumatic stress (a), depression (b), and pain (c), controlling for all other factors in the model. Error bars represent standard errors. ASDS = Acute Stress Disorder Scale total score; DASS-D = Depression Anxiety Stress Scale 21-item depression subscale score; pain = subjective pain rating, NRD = non-relevant distraction; RD = relevant distraction; STD = standard. * $p < .05$.

Accuracy

Figure 3 displays the estimated marginal means of extended Ruff 2 & 7 accuracy scores obtained from the MANOVAs at the ASDS total mean (and one standard deviation above and below) as well as at the means of DASS-D scores, and pain ratings (and one standard deviation above and below), holding constant all other factors. MANOVA results revealed significant large main effects of acute post-traumatic stress, $F(1, 37) = 21.54$, $p <$ .001, $\eta_p^2 = .37$, and depression, $F(1, 37) = 8.13$, $p = .007$, $\eta_p^2 = .18$, on accuracy. More severe acute post-traumatic stress symptoms were associated with lower accuracy scores whereas more severe depressive symptoms were associated with higher accuracy scores. Pain did not show a significant main effect on accuracy, $F(1, 37) = 1.90$, $p = .18$, $\eta_p^2 = .05$. In terms of accuracy, there were no significant interactions between increasing cognitive demands and acute post-traumatic stress, $F(2, 36) = 2.40$, $p = .11$, $\eta_p^2 = .12$; depression, $F(2, 36) = 0.59$, $p =$ .56, $\eta_p^2 = .03$; or pain, $F(2, 36) = 1.49$, $p = .24$, $\eta_p^2 = .08$. Scatterplots of the untransformed data confirmed the direction of these relationships (Figure C2, Appendix C).

Mental Effort Ratings

Subjective mental effort ratings showed a large main effect of depression, $F(1, 37) =$ 12.08, $p = .001$, $\eta_p^2 = .25$, and a medium to large main effect of pain, $F(1, 37) = 4.53$, $p = .040$, $\eta_p^2 = .11$. As displayed in Figure 4, participants with greater severity of depressive symptoms reported lower ratings of mental effort and those with greater pain reported higher ratings of mental effort. There was no significant main effect of acute post-traumatic stress, $F(1, 37) =$ 0.67, $p = .42$, $\eta_p^2 = .02$. There were no significant interactions between acute post-traumatic stress, $F(2, 36) = 0.09$, $p = .92$, $\eta_p^2 < .01$; depression, $F(2, 36) = 0.20$, $p = .82$, $\eta_p^2 = .01$; or pain, $F(2, 36) = 1.04$, $p = .36$, $\eta_p^2 = .06$, and change in mental effort ratings across the task conditions.
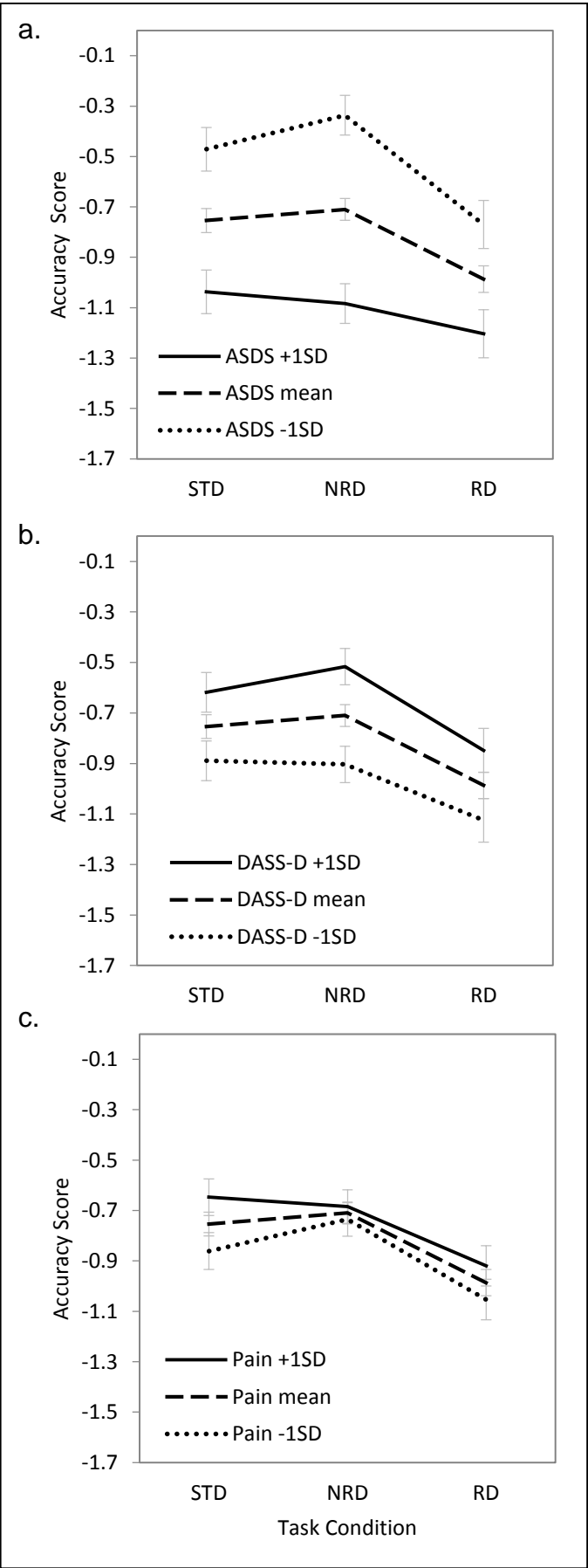
Figure 3. Extended Ruff 2 & 7 accuracy in each task condition at mean levels (and one standard deviation above and below the mean) of acute post-traumatic stress (a), depression (b), and pain (c) controlling for other factors. Error bars represent standard errors. ASDS = Acute Stress Disorder Scale total score; DASS-D = Depression Anxiety Stress Scale 21-item depression subscale score; pain = subjective pain rating; NRD = non-relevant distraction; RD = relevant distraction; STD = standard.
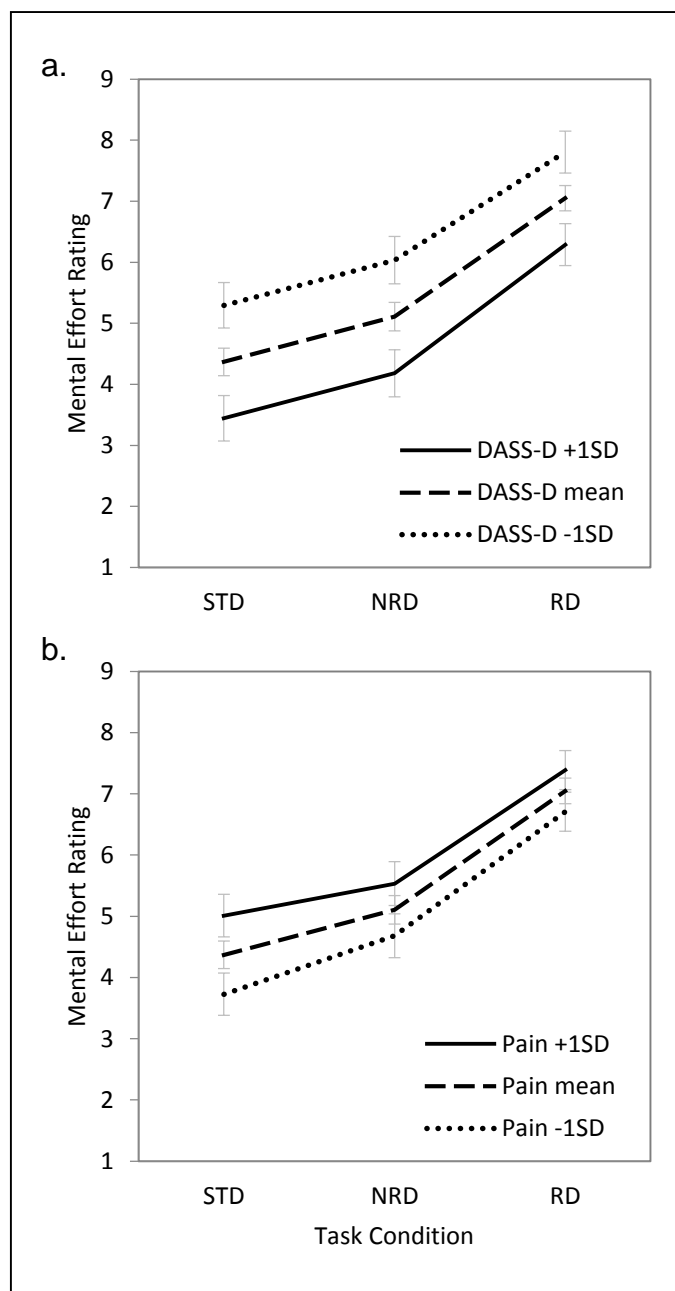
Figure 4. Mental effort ratings in each task condition at mean levels (and one standard deviation above and below the mean) of depression (a), and pain (b) controlling for other factors. Error bars represent standard errors. DASS-D = Depression Anxiety Stress Scale 21-item depression subscale score; pain = subjective pain rating; NRD = non-relevant distraction; RD = relevant distraction; STD = standard.

Influence of Self-Reported Psychiatric History and Opioids

Self-reported psychiatric history had no significant main or interaction effects when included in the speed, accuracy, and mental effort rating analyses. Including psychiatric history had no impact on the significance or magnitude of the associations of acute post-traumatic stress, depression, and pain, with speed, accuracy, or mental effort ratings.

Opioid intake in the 24 hours prior to assessment was not significantly correlated with subjective pain ratings, $r = .19$, $p = .22$, speed scores (STD, $r = -.03$, $p = .87$; NRD, $r = -.07$, $p = .68$; RD, $r = -.20$, $p = .21$), nor accuracy scores (STD, $r = -.17$, $p = .29$; NRD, $r = -.19$, $p = .24$; RD, $r = -.23$, $p = .14$). Opioid intake was not significantly correlated with mental effort ratings in the STD, $r = .25$, $p = .11$, nor NRD, $r = .21$, $p = .18$, conditions but was positively correlated with mental effort ratings in the RD condition, $r = .41$, $p = .007$.

Opioid intake in the preceding 24 hours showed no significant main, $F(1, 36) = 0.72$, $p = .40$, $\eta_p^2 = .02$, or interaction effect $F(2, 35) = 2.08$, $p = .14$, $\eta_p^2 = .11$, on speed scores. Opioid intake had a medium to large main effect on accuracy, $F(1, 36) = 5.08$, $p = .030$, $\eta_p^2 = .12$. Intake of opioids was associated with lower accuracy scores (Figure 5a). There was no interaction between opioid intake and change in accuracy across task conditions, $F(2, 35) = 0.15$, $p = .87$, $\eta_p^2 = .01$. Inclusion of opioid intake had no notable impact on the significance or magnitude of the associations of acute post-traumatic stress, depression, or pain with speed or accuracy scores. Opioid intake had a significant large main effect on mental effort ratings, $F(1, 36) = 5.64$, $p = .023$, $\eta_p^2 = .14$. Opioid intake was associated with higher ratings of mental effort (Figure 5b). There was no interaction between opioid intake and change in mental effort ratings across task conditions, $F(2, 35) = 0.76$, $p = .48$, $\eta_p^2 = .04$. Inclusion of opioid intake also had no notable impact on the significance or magnitude of the associations of acute post-traumatic stress, depression, or pain with mental effort ratings, with the exception of the main effect of pain, which was rendered non-significant $F(1, 36) = 3.00$, $p = .092$, and mildly reduced in magnitude, $\eta_p^2 = .08$.
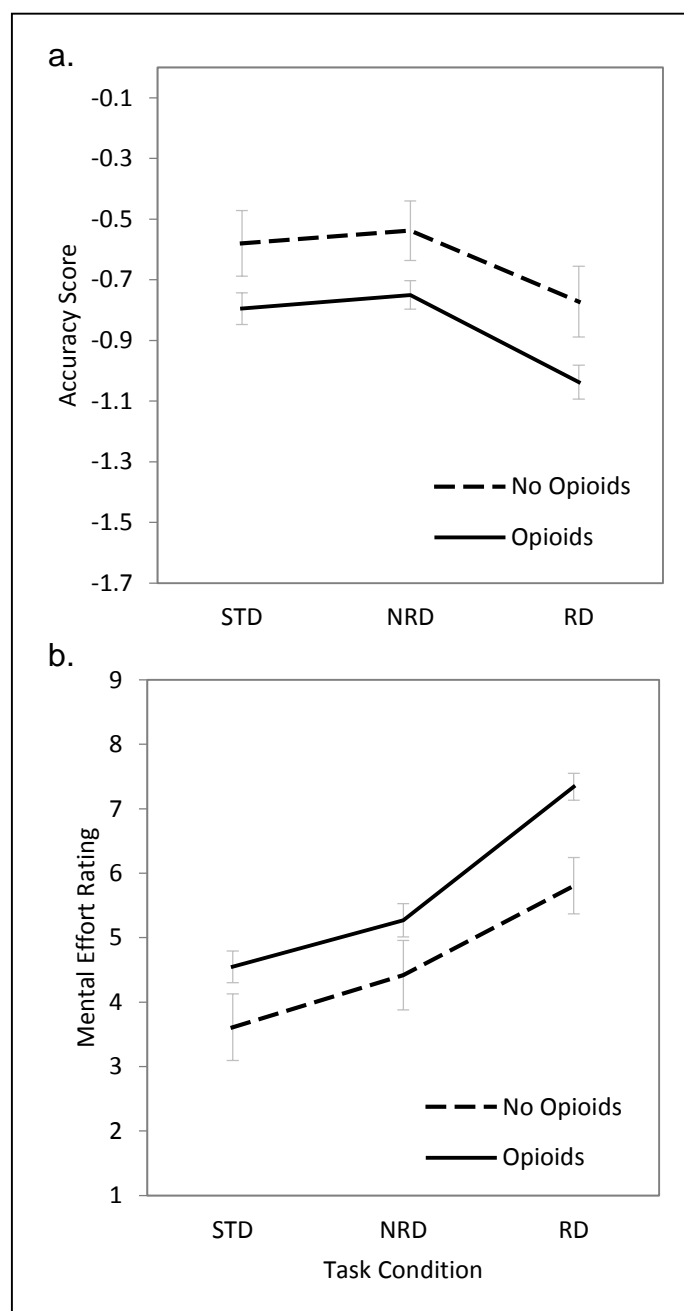
Figure 5. Extended Ruff 2 & 7 accuracy (a) and mental effort ratings (b) in each task

condition in participants who had or had not been administered opioids in the 24 hours prior

to assessment. Error bars represent standard errors. NRD = non-relevant distraction; RD =

relevant distraction; STD = standard.

Discussion

The first aim of the current study was to examine whether acute post-traumatic stress, depression, and pain were associated with cognitive performance on an attentional task in adult trauma patients in the acute to sub-acute phase following mTBI. The second aim was to examine whether these associations interacted with increasing cognitive demands. The study additionally explored whether psychological distress and pain were related to patients' subjective experience of mental effort. Lastly, the influences of self-reported psychiatric history and recent opioid intake on the results were investigated.

Acute post-traumatic stress and depression demonstrated contrasting associations with accuracy, partially supporting the first hypothesis that acute post-traumatic stress, depression, and pain would be associated lower scores on speed and accuracy measures on the extended Ruff 2 & 7 task. Acute post-traumatic stress, depression, and pain also had unique associations with speed performance as task demands increased, partially supporting the second hypothesis that these factors would be associated with larger declines in performance as cognitive demands increased. There was also partial support for the third hypothesis: Participants' ratings of mental effort were related to depression and pain but not to acute post-traumatic stress. Controlling for self-reported psychiatric history and recent opioid intake did not significantly alter the associations of acute post-traumatic stress, depression, or pain with cognitive performance. Self-reported psychiatric history showed no significant associations with attentional performance or mental effort ratings. Recent opioid intake was associated with accuracy and mental effort ratings but not speed performance. Due to the distinct results of acute post-traumatic stress, depression, and pain, the findings regarding each factor will be discussed separately.

Acute post-traumatic stress was not significantly associated with overall speed but was related to significantly lower overall accuracy. Acute post-traumatic stress was also related to greater declines in speed as cognitive demands increased but not to changes in accuracy as

demands increased. These findings provide partial support for the first hypothesis that more severe acute post-traumatic stress would be associated with lower speed and accuracy scores following mTBI. They also provide partial support for the second hypothesis that this association would interact with cognitive demands, at least in terms of speed. These data are generally consistent with resource theories of anxiety such as the attentional control theory (Derakshan & Eysenck, 2009; Eysenck et al., 2007). The data support the proposal that anxiety is associated with both lower attentional performance and greater declines in performance as cognitive demands increase. The data extend previous findings which suggest that anxiety moderates cognitive performance within the acute to sub-acute phase of mTBI (Batchelor et al., 1995).

Contrary to the first hypothesis, depression showed no association with overall speed, and greater severity of depressive symptoms was associated with higher accuracy scores. Also opposing the second hypothesis, more severe depressive symptomatology was associated with smaller declines in speed as cognitive demands increased. Those with more severe depressive symptoms also reported requiring less mental effort to complete the task compared to those with less severe depressive symptoms. These results suggest that depression may not always consume resources otherwise required for cognitive performance (Ellis & Ashbrook, 1988). The current data appear consistent with other literature suggesting that individuals with depressive symptoms may show a systematic and focused style of processing that benefits accuracy and attentional control (Andrews & Thomson, 2009; Zwosta, Hommel, Goschke, & Fischer, 2013), particularly when they are faced with greater demands or are sufficiently engaged in the task (Hertel & Rude, 1991; Schnabel & Kydd, 2012). Similar to the current results, Schnabel and Kydd (2012) found that performance on attention and encoding measures in outpatients with depression improved in the presence of auditory distraction. Notably, Schnabel and Kydd also assessed a mTBI group around three months post-injury but they did not find any improvement in their performance when faced

with distraction. Nor did they find any relationship between self-reported depressive symptoms and change in mTBI participants' cognitive performance from standard to distraction conditions (Schnabel & Kydd, 2012). In contrast to Schnabel and Kydd's results, Ghaffar, McCullagh, Ouchterlony and Feinstein (2006) found that depressive symptoms were related to significantly lower cognitive performance in a number of domains in a sample of consecutive mTBI trauma patients tested 6 months post-injury. The discrepancy between the findings of these post-acute studies (Ghaffar et al., 2006; Schnabel & Kydd, 2012) and the current results may be related to differences in the periods between mTBI and assessment and/or the use of different cognitive measures. The current findings of higher accuracy scores in individuals with more severe depressive symptoms also contrast with Preece and Geffen's (2007) results of worse cognitive performance in mTBI patients with pre-existing depression tested in the acute phase. However, Preece and Geffen's participants showed lower performance on a measure of a verbal recognition which was not measured in the current study. Additionally, because Preece and Geffen aimed to investigate pre-existing depression, patients were not required to report current depressive symptoms. Thus, their results may be specific to patients with pre-existing depression rather than patients experiencing acute depressive symptoms.

The findings regarding pain differed from the patterns observed in both acute post-traumatic stress and depression. In opposition to the first hypothesis, pain was not associated with overall speed or accuracy. Partially supporting the second hypothesis, more severe pain was associated with a larger decline in speed but not accuracy as cognitive demands increased. Greater difficulty in the presence of more severe pain was also reflected in participants' subjective reports of increased mental effort during the task. The results were generally consistent with existing resource theories of pain (Eccleston & Crombez, 1999; Grigsby et al., 1995; Legrain et al., 2009; Sanchez, 2011), and empirical findings suggesting that acute pain is associated with lower cognitive performance (Etherton, Bianchini, Heinly,

& Greve, 2006; D. J. Moore et al., 2013; Sanchez, 2011). The current findings extend the existing literature (e.g., Beaupré et al., 2012) by suggesting that an association between pain and cognitive functioning may be present within the first 2 weeks of recovery from mTBI.

Investigation of two potentially moderating factors—self-reported psychiatric history and opioid intake—found little impact on the abovementioned results, although opioid intake in the preceding 24 hours showed independent associations with lower cognitive performance, consistent with previous research (Meares et al., 2006; Zacny, 1995). Further research using more comprehensive measures of psychiatric history (e.g., structured clinical interviews) will be useful to confirm whether this factor may play a role in associations among distress, pain, and cognition following mTBI.

Factors other than neurological injury have been frequently overlooked in studies of cognitive outcome following mTBI (Alexander, 1995; Carroll, Cassidy, Holm, et al., 2004; Larrabee, Binder, Rohling, & Ploetz, 2013). The present study represents a thorough attempt to investigate whether psychological distress and pain are associated with cognitive functioning in the acute to sub-acute phase following mTBI. By controlling for comorbidity, contrasting associations were revealed between these variables. It is acknowledged, however, that these symptoms may overlap with each other and with other mTBI sequelae (Brown, Chorpita, Korotitsch, & Barlow, 1997; Gross & Collins, 1981; Iverson, 2006; Iverson & McCracken, 1997; Mounce, Keogh, & Eccleston, 2010; Shackman et al., 2011). For instance, dissociative symptoms assessed by the ASDS may overlap with residual symptoms of the brain injury (Grigsby & Kaye, 1993; Jones, Harvey, & Brewin, 2005; O'Donnell et al., 2003). For example, amnesia reported by mTBI patients for aspects of the traumatic event may be due to psychological trauma, PTA, or the effect of opioids (Jones et al., 2005; O'Donnell et al., 2003). Although the current study excluded the ASDS item that measures amnesia, it remains possible that other dissociative items—which were commonly reported symptoms on the ASDS—were related to the effects of brain injury or opioids. These factors may have

contributed to the associations observed between acute post-traumatic stress and lower

cognitive performance (Broomhall et al., 2009; Jones et al., 2005; Meares et al., 2006).

Similarly, attentional tasks are multifaceted and require multiple cognitive abilities for

successful performance (Derakshan & Eysenck, 2009; Lezak, Howieson, Bigler, & Tranel,

2012; van Zomeren & Brouwer, 1992). The precise mechanisms behind the current results

therefore require further delineation.

Nevertheless, by using an attentional task that manipulated the level of cognitive

demands (Cicerone, 1996), differences were elicited as cognitive demands increased. These

interactions reveal that psychological distress and pain may be related to how mTBI patients

respond to changing cognitive demands. In terms of pain, significant associations with

cognitive performance (i.e., speed) were only detected as scores changed across task

conditions. Such tasks also arguably have greater ecological validity in terms of a patient's

daily functioning (Mateer & Mapou, 1996).

A strength of the present study included the prospective recruitment of consecutive

trauma admissions, increasing the likelihood the sample was representative and thereby the

generalizability of results. Although mTBI samples typically include a greater proportion of

males (Cassidy et al., 2004; Feigin et al., 2013; Leibson et al., 2011; Sosin, Sniezek, &

Thurman, 1996), the current sample included more males compared to other recently recruited

mTBI trauma samples (Bryant et al., 2010; Faux et al., 2011; Feigin et al., 2013; Levin et al.,

2013; Ponsford et al., 2011), highlighting the need for replication of the current findings.

The current study did not include a traumatically non-brain injured control group.

Consequently, the current conclusions are limited to a mTBI sample. The design of the

present study also precluded conclusions regarding causality. Prospective longitudinal studies

of trauma samples including appropriate control groups are required to examine causality and

specificity. The small sample size in the current study reduced statistical power and the

ability to detect more subtle associations. Conversely, as alpha levels were not corrected for

multiple comparisons due to the exploratory nature of the investigation, there remains the possibility of Type I error. The physical requirements of the Ruff 2 & 7 also required some participants with dominant arm injuries to be excluded. The collection of data in future studies may benefit from using tasks less reliant on physical status.

The current results raise the possibility of complex associations of acute post-traumatic stress, depression, and pain with cognitive functioning during recovery from mTBI. These relationships may interact with changing levels of cognitive demand. Psychological distress and pain should be considered in the differential diagnosis of mTBI patients in clinical settings and outcome studies. Furthermore, cognitive functioning may be particularly important to evaluate in those with high levels of psychological distress or pain. Recovery from mTBI may be optimized by addressing both psychological and cognitive functioning. Future research is required to replicate and further investigate these findings. Attentional measures or tasks that incorporate increasing cognitive demands may prove helpful in the investigation of these associations.

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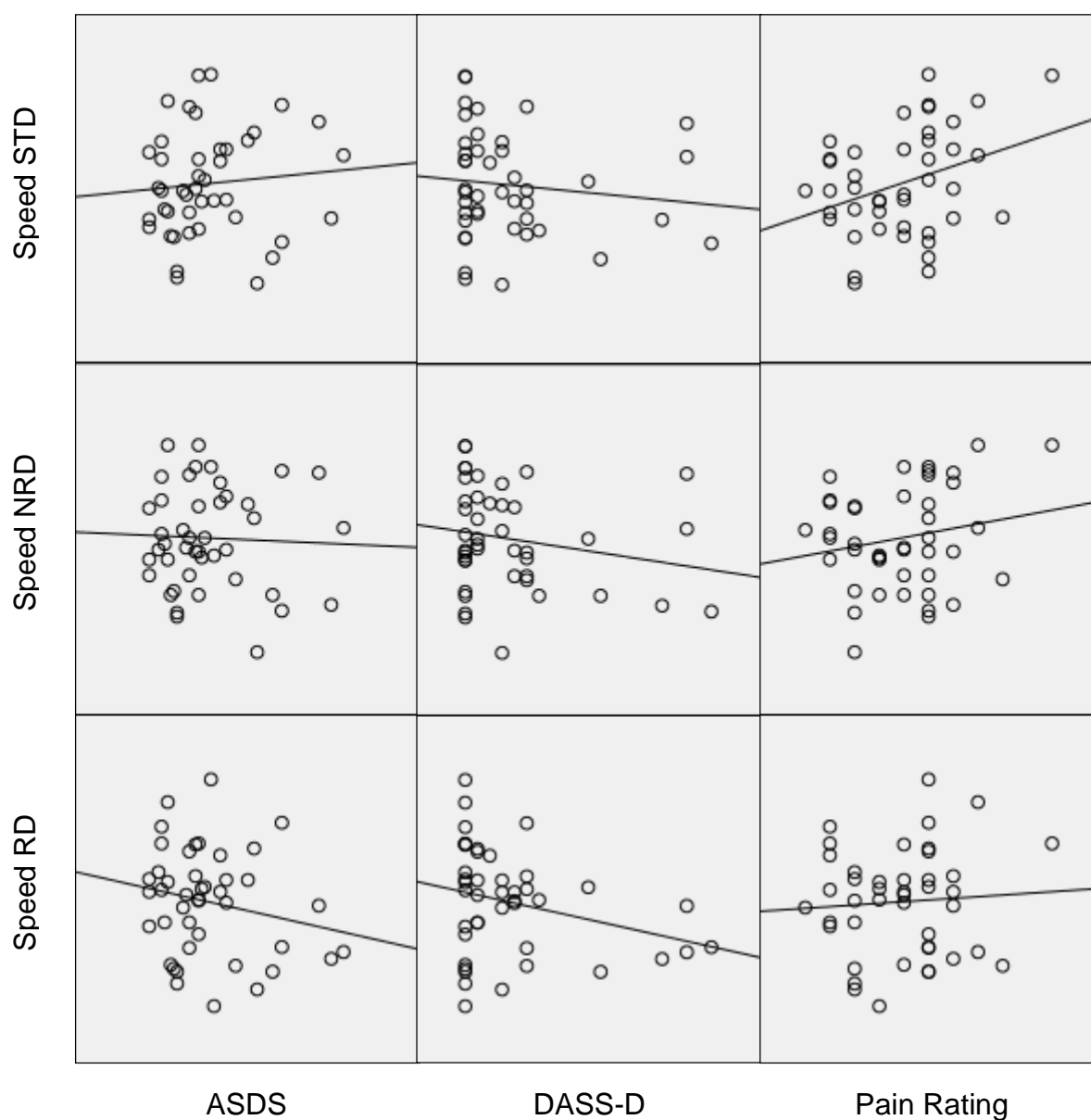
Appendix C

Figure C1. Scatterplots of the relationships between the untransformed variables of Acute Stress Disorder Scale (ASDS) total scores, Depression Anxiety and Stress Scale 21-item depression subscale (DASS-D) scores, subjective pain ratings, and extended Ruff 2 & 7 speed scores under standard (STD), non-relevant distraction (NRD), and relevant distraction (RD) conditions.
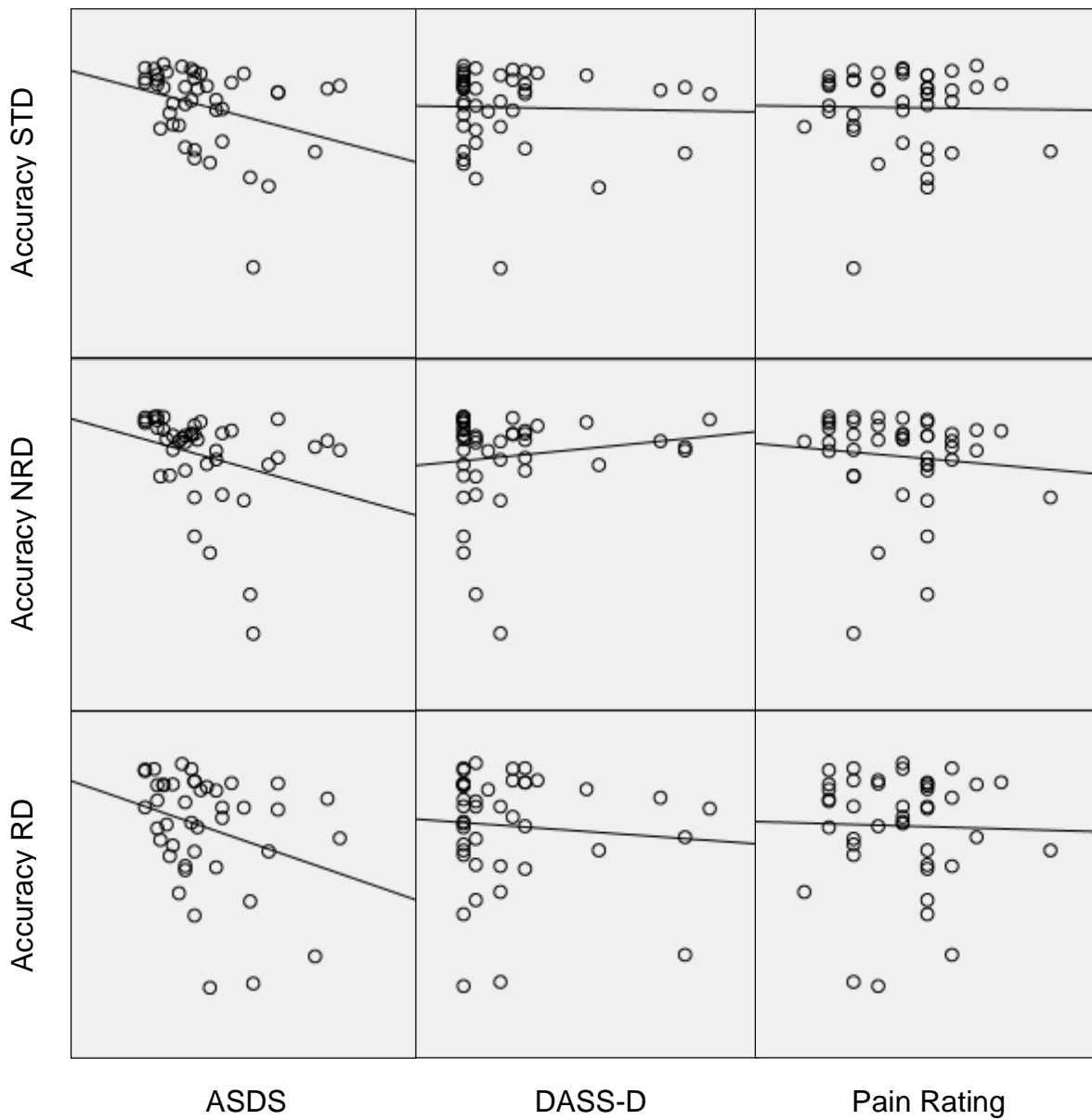
Figure C2. Scatterplots of the relationships between the untransformed variables of Acute

Stress Disorder Scale (ASDS) total scores, Depression Anxiety and Stress Scale 21-item

depression subscale (DASS-D) scores, subjective pain ratings, and extended Ruff 2 & 7

accuracy scores under standard (STD), non-relevant distraction (NRD), and relevant

distraction (RD) conditions.

Chapter 5

General discussion

General Discussion

The current research aimed to investigate the associations of psychological distress and pain with cognitive functioning following mild traumatic brain injury (mTBI). The specific objectives were to (i) systematically review the existing evidence regarding the relationship between psychological distress and cognitive functioning following mTBI in adults, (ii) explore whether acute post-traumatic stress, depression, and pain were associated with cognitive performance in a number of cognitive domains (including attention, memory, processing speed, reaction time, working memory, and verbal fluency) in adult trauma patients in the acute to sub-acute phase of mTBI, (iii) further evaluate whether acute post-traumatic stress, depression, and pain were associated with cognitive performance on the extended version (Cicerone, 1996) of the Ruff 2 & 7 Selective Attention Test (Ruff & Allen, 1996), (iv) examine whether the associations of acute post-traumatic stress, depression, and pain to performance on the extended Ruff 2 & 7 differed as cognitive demands increased, (v) evaluate whether acute post-traumatic stress, depression, and pain were related to subjective ratings of mental effort expended during completion of the extended Ruff 2 & 7, and (vi) assess whether self-reported psychiatric history and recent opioid intake were related to the associations of psychological distress and pain with cognitive performance.

A discussion of the results of the current research follows: The first section discusses the results of the systematic review (Study 1) and the second section discusses the results of the empirical investigations (Studies 2 and 3).

Systematic Review of the Relationship between Psychological Distress and Cognitive Functioning following MTBI

Summary of the findings. The systematic review comprising Study 1 identified 17 studies that examined the relationship between psychological distress and cognitive functioning following mTBI. Application of a critical appraisal tool (Heacock, Koehoorn, & Tan, 1997) and evidence hierarchy (National Health and Medical Research Council

[NHMRC], 2009) revealed that the quality of the evidence was limited. Only two studies used prospective longitudinal designs, the highest level of empirical evidence (Durazzo et al., 2013; Ghaffar, McCullagh, Ouchterlony, & Feinstein, 2006). Most studies did not use representative sampling methods or settings, or traumatically non-brain injured control groups. The authors of many studies incompletely reported the study design, methodology, statistical analysis, power, and statistical significance level. Furthermore, the use of small samples and a lack of consideration of confounding factors (e.g., litigation, suboptimal effort, comorbid forms of distress, and comorbid pain) were also identified as weaknesses in the existing research. The designs and methodologies of the reviewed studies did not allow for conclusions regarding causal relationships and possible mechanisms underlying associations between psychological distress and cognitive functioning following mTBI. Additionally, because most studies did not include traumatically non-brain injured controls, the specificity of results to mTBI could not be determined. The study with the strongest methodology and design used a prospective longitudinal design to recruit a relatively large sample of consecutive mTBI admissions from multiple trauma centers (Ghaffar et al., 2006). The authors reported significantly lower performance on measures of attention, reaction time, and non-verbal abstract reasoning at 6 months post-injury in mTBI participants who reported depressive symptoms compared to those who reported no depressive symptomatology (Ghaffar et al., 2006).

Methodological strengths and limitations. The systematic review comprised a comprehensive effort to summarize the evidence published over the last 18 years regarding the relationship between psychological distress and cognitive functioning following mTBI. Nevertheless, due to the exclusion of unpublished literature, literature published in dissertation databases, and literature published in languages other than English, publication bias may have influenced the results (Rosenthal, 1979). Similarly, depression may have been more likely to have been associated with cognitive impairment following mTBI simply

because depressive symptoms were more likely to be measured than other types of distress. Other forms of psychological distress, such as anxiety and post-traumatic stress were less frequently measured. Consequently, the evidence regarding their relationship with cognitive functioning after mTBI remains limited.

The use of a critical appraisal tool (Heacock et al., 1997) and evidence hierarchy which ranked study designs in terms of their strength in addressing the research question (NHMRC, 2009) enabled systematic evaluation of the quality of the methodology and design of the literature. These evaluations illuminated the areas of weakness in the existing research and, by doing so, highlighted areas to be addressed by future investigations. The weaknesses of the reviewed studies were consistent with those previously identified as problematic in mTBI research (Carroll, Cassidy, Holm, Kraus, & Coronado, 2004).

Implications. This systematic review highlights the possibility that individuals experiencing psychological distress, particularly depressive symptoms, may demonstrate greater cognitive dysfunction following mTBI. The results underscore the need to consider psychological distress in the neuropsychological assessment of mTBI patients in both clinical and research settings. Additionally, the results emphasize the need for further research, particularly studies using prospective consecutive trauma samples which consider the influence of confounding factors—including comorbid distress and pain, suboptimal effort, and litigation—using multivariate statistical methods.

Empirical Investigations Regarding the Associations of Psychological Distress and Pain with Cognitive Functioning in the Acute to Sub-Acute Phase following MTBI

Summary of the findings. In Study 2, the results from canonical correlation analyses (CCAs) indicated that, of the cognitive domains (attention, memory, processing speed, reaction time, working memory, and verbal fluency) and psychological factors (acute post-traumatic stress, depression, and pain) measured, only performance on the extended Ruff 2 & 7 task (Cicerone, 1996; Ruff & Allen, 1996) showed significant associations with acute post-

traumatic stress and pain in mTBI patients assessed within 14 days of injury. Consistent with expectations, acute post-traumatic stress was associated with lower accuracy scores across task conditions. Unexpectedly, acute post-traumatic stress and pain were both associated with higher speed scores under non-distracting conditions and to a lesser degree, lower speed scores in the presence of an auditory distraction. Scatterplots of raw data confirmed the direction of these unexpected relationships (see Chapter 3, Appendix B, Figures B1 and B2). The role of depressive symptoms remained unclear although depression appeared to contribute to the latent variables by reducing redundancy among the psychological measures.

Based on multivariate analyses of variance (MANOVAs), the results from Study 3 further revealed that acute post-traumatic stress, depression, and pain were distinctly associated with speed and accuracy performance on the extended Ruff 2 & 7 task. The analyses also uncovered unique interactions between acute post-traumatic stress, depression, and pain, and speed performance across increasing levels of cognitive demand. Consistent with the hypotheses, more severe acute post-traumatic stress was associated with lower accuracy and greater declines in speed as cognitive demands increased. Unexpectedly, more severe depressive symptoms were associated with higher accuracy and smaller declines in speed as cognitive demands increased. Scatterplots of the raw data confirmed the direction of these unexpected relationships (see Chapter 4, Appendix C). Pain was not associated with accuracy but more severe pain was related to greater declines in speed with increasing cognitive demands. Participants also subjectively rated the degree of mental effort they required to complete the task. While more severe depressive symptoms were associated with lower ratings of mental effort, more severe pain was associated with higher ratings of mental effort. Acute post-traumatic stress showed no significant associations with mental effort ratings. Opioid intake in the 24 hours prior to assessment and self-reported psychiatric history did not appear to account for the observed associations of acute post-traumatic stress, depression, and pain to performance on the extended Ruff 2 & 7 task although opioid intake

did appear to be independently associated with lower accuracy scores and greater mental effort ratings.

There was inconsistency between the results obtained in Studies 2 and 3. In contrast to the results from Study 2, the results from Study 3 did not reveal significantly higher speed scores in the presence of acute post-traumatic stress or pain. It is possible the different statistical methods used in each study were differentially sensitive to relationships amongst variables, leading to different results. For example, the CCAs of Study 2 detected the strongest associations between the psychological factors and performance on each of the individual task conditions of the extended Ruff 2 & 7 task. It is possible that Study 3 did not find main effects of higher speed scores in the presence of acute post-traumatic stress and pain because the tests of these effects considered performance across all task conditions simultaneously. Furthermore, while depression showed relationships with accuracy and change in speed performance across task conditions in the results from the MANOVAs conducted in Study 3, the CCAs reported in Study 2 did not find any significant associations between depressive symptoms and cognitive performance. These discrepancies may also be attributable to the use of different statistical analyses: the CCAs in Study 2 may not have had sufficient statistical power in the current sample to detect an association of depression with cognitive performance in addition to the associations of acute post-traumatic stress and pain. Alternatively, it is possible that some of the current results reflect Type I or Type II errors.

The results of these empirical studies extend the existing literature regarding the relationship between psychological distress and cognitive functioning following mTBI. The results regarding acute post-traumatic stress obtained in Studies 2 and 3 extend those of Batchelor, Harvey, and Bryant (1995), which suggested that anxiety modulates mTBI patients' attentional performance. The current results further suggest that acute post-traumatic stress may be associated with lower accuracy as well as variable speed during the completion of an attentional task. The results contrast with those of Durazzo et al. (2013) and

Suhr and Gunstad (2002) who reported no effect of anxiety symptoms on cognitive functioning following mTBI. These discrepancies may be attributable to methodological differences. While Durazzo et al. (2013) and Suhr and Gunstad (2002) measured state anxiety, the current study measured acute post-traumatic stress. The studies also differed in statistical methods, time between mTBI and assessment, and the potential sensitivity of cognitive and/or psychological measures. The current results also further elaborate on the existing mTBI literature by suggesting that the association between acute post-traumatic stress and cognitive performance following mTBI may interact with the level of cognitive demand. The current findings of lower accuracy and the greater declines in speed scores with increasing cognitive demands in the presence of acute post-traumatic stress are consistent with attentional control theory and empirical findings indicating a detrimental effect of anxiety on cognitive functioning (Castaneda, Tuulio–Henriksson, Marttunen, Suvisaari, & Lönnqvist, 2008; Eysenck, Derakshan, Santos, & Calvo, 2007; Johnsen & Asbjørnsen, 2008). Higher speed scores in the presence of acute post-traumatic stress under less demanding conditions, however, was not expected on the basis of this literature. Further discussion of this unexpected result is provided below in conjunction with the results regarding pain.

The current results provide further evidence of the relationship between depressive symptoms and cognitive functioning following mTBI. The results of Study 2 are generally consistent with those of Preece and Geffen (2007) who reported no influence of pre-existing depression on verbal learning, verbal recall, or processing speed in the acute phase of mTBI (although they did detect an association between pre-existing depression and reduced verbal recognition which was not measured in the current study). Study 3 further indicates that participants with more severe depressive symptoms may demonstrate higher cognitive performance in the acute to sub-acute phase of mTBI, at least on tasks of attentional functioning, and that this relationship may interact with cognitive demand. The results of Study 3 contrast with results obtained by Ghaffar and colleagues (2006) who reported lower

performance in various cognitive domains (including attention, reaction time, and non-verbal abstract reasoning) amongst mTBI trauma patients reporting depressive symptoms at 6 months post-injury. Their opposing results may be due to the use of different cognitive and psychological measures, or the longer interval between injury and assessment which could moderate distress–cognition relationships. Although the unexpected results regarding depression in Study 3 contrast with literature suggesting negative effects of depressive symptoms on cognition (Castaneda et al., 2008; Lee, Hermens, Porter, & Redoblado–Hodge, 2012), they are consistent with other findings indicating improved attentional focus in depression (Andrews & Thomson, 2009; Zwosta, Hommel, Goschke, & Fischer, 2013).

The current findings also provide preliminary evidence regarding the association between pain and cognitive functioning in the acute to sub-acute phase following mTBI. The significant associations observed between pain and speed performance in Studies 2 and 3 contrast with other mTBI studies which found no significant association between pain and neuropsychological performance in mTBI patients (Jamora, Schroeder, & Ruff, 2013; Landre, Poppe, Davis, Schmaus, & Hobbs, 2006; Tsushima & Newbill, 1996). However, Landre et al.'s (2006) analysis grouped trauma patients with mTBI together with those who had not sustained mTBI and Jamora et al.'s (2013) and Tsushima and Newbill's (1996) samples consisted of referred mTBI outpatients. Those samples may have therefore differed from the current sample in the types of injury and degree of representativeness in terms of the hospitalized mTBI population. While the greater declines in speed with increasing demands observed in patients with more severe pain in Study 3 are generally consistent with resource theories of pain's detrimental effect on cognition (Eccleston & Crombez, 1999; Legrain et al., 2009; Sanchez, 2011), higher speed scores under non-distracting conditions in Study 2 was not expected on the basis of these theories and existing research (Eccleston & Crombez, 1999; Hart, Martelli, & Zasler, 2000; Legrain et al., 2009; Moriarty, McGuire, & Finn, 2011; Nicholson, 2000; Sanchez, 2011).

As mentioned above, the results of higher speed scores in the presence of more severe acute post-traumatic stress and pain are inconsistent with resource theories (Eccleston & Crombez, 1999; Eysenck et al., 2007; Legrain et al., 2009; Sanchez, 2011). It is possible that increased physiological arousal may explain these unexpected findings. Both anxiety and pain have been associated with increased sympathetic nervous system activity (Bremner, Krystal, Southwick, & Charney, 1996; Chapman & Nakamura, 1999; Felmingham, Rennie, Gordon, & Bryant, 2012; Jänig, 1995), which in turn may facilitate attentional processes (Duschek, Muckenthaler, Werner, & Reyes del Paso, 2009; see also Berntson, Sarter, & Cacioppo, 2006; Coull, 1998) and motor readiness (Jänig, 1995; Zwosta et al., 2013). Alternatively, the unexpected findings may suggest that the patterns observed in the existing literature may not apply to individuals in the acute to subacute stage of mTBI recovery. Further research is required to investigate this possibility and the mechanisms behind associations of acute post-traumatic stress and pain with higher speed performance.

Mental effort ratings in the current research were not found to be consistently concordant with the cognitive performance of the mTBI participants. In other words, it appeared that participants' subjective experience of the effort they required to complete the task did not always correspond to their objective performance (e.g., whereas those with more severe acute post-traumatic stress showed lower accuracy on the extended Ruff 2 & 7 task, they did not rate their mental effort as greater on this task compared with participants reporting less severe acute post-traumatic stress). Mental effort ratings may reflect self-perceived cognitive efficiency (Paas, 1992). The current findings appear consistent with suggestions that cognitive efficiency may not always correspond to absolute performance levels in mTBI (e.g., McAllister et al., 1999; 2001). Alternatively, mental effort ratings may also indicate motivation levels (Paas, 1992). While screening of effort using embedded measures in the current study did not indicate suboptimal effort in any participant, more subtle fluctuations in motivation were possible and may have been reflected in mental effort

ratings. Regardless, it is unclear why participants who reported more severe acute post-traumatic stress, depression, and pain differed in their ratings of mental effort. It is possible that depressive symptoms and pain may be associated with individuals' attributions regarding cognitive performance, whereas acute post-traumatic stress symptoms may not hold strong relationships to participants' attributions or experience of mental effort.

The observed associations between opioid intake and lower cognitive performance are consistent with a previous study conducted in the acute to sub-acute phase of mTBI (Meares et al., 2006). Meares et al. found that opioid intake was correlated with reduced verbal learning. The current findings suggest that opioid intake may additionally affect mTBI patients' accuracy on attentional measures. The sedative effects of opioid analgesia (Schug, 2013) may contribute to lower accuracy on attentional tasks.

Methodological strengths and limitations. Overall, the empirical studies addressed a number of methodological issues identified in the systematic review as being deficient in the existing literature. One of these strengths was the prospective recruitment of a consecutive trauma sample from a Level 1 trauma setting, which increased the likelihood that the sample was representative of the hospitalized mTBI population and therefore the generalizability of results. Despite this effort, there were more males in the current sample compared to recent mTBI trauma samples (e.g., Bryant et al., 2010; Levin et al., 2013) and epidemiological estimates (Feigin et al., 2013; Leibson et al., 2011).

Another strength of Studies 2 and 3 was the inclusion of measures of various forms of psychological distress (acute post-traumatic stress and depression), current pain intensity, and several cognitive domains (attention, memory, processing speed, reaction time, working memory, and verbal fluency), which allowed a comprehensive investigation of these relationships. A related strength was the use of a neuropsychological task that incorporated increasing levels of cognitive demand (i.e., the extended Ruff 2 & 7 task; Cicerone, 1996). Inclusion of this task provided sufficient sensitivity for detecting associations among

psychological distress, pain, and cognition in a modestly sized sample. Using the extended Ruff 2 & 7 task also permitted novel investigations into the interactions of psychological distress and pain with increasing cognitive demands. Such investigations may be particularly pertinent to the real-life challenges faced by mTBI patients as they recover and return to functional activities (Mateer & Mapou, 1996). It is acknowledged that the measures of psychological distress and cognitive functioning used in the current research may not have represented pure constructs (Derakshan & Eysenck, 2009; Grigsby & Kaye, 1993; Iverson, 2006; Iverson & McCracken, 1997; Jones, Harvey, & Brewin, 2005; O'Donnell, Creamer, Bryant, Schnyder, & Shalev, 2003; van Zomeren & Brouwer, 1992). Such overlap may have contributed to observed associations of psychological distress and pain with cognitive performance.

The small sample reduced the statistical power of the empirical studies. The modest sample size may have detected only very large effects and prevented detection of more subtle associations. This suggestion is supported by the medium to large but non-significant percent of variance shared between psychological and cognitive measures such as the Computerized Test of Information Processing in Study 2. In order to preserve the participant-to-variable ratio and maximize statistical power, separate analyses were conducted, however, this may have increased the risk of Type I error. On the contrary, a strength of the research was the use of multiple statistical methods, which in Study 3 enabled detection of other relationships among the psychological and cognitive variables that were not identified in Study 2. The use of multivariate statistical methods revealed the unique associations between the highly comorbid psychological factors (of acute post-traumatic stress, depression, and pain) and cognitive performance in mTBI patients. Multivariate analyses also enabled the evaluation of potentially confounding factors (self-reported psychiatric history and opioid intake). Contrary to the majority of the literature reviewed in Study 1, the inclusion of multiple embedded effort measures allowed for the consideration of and exclusion of participants with suboptimal

effort. It is acknowledged, however, that although both effort measures have been validated for use in mTBI (Millis, Putnam, Adams, & Ricker, 1995; Willison & Tombaugh, 2006; see also Greve, Curtis, Bianchini, & Ord, 2009), these measures have not been previously applied in an acute to sub-acute mTBI sample. Future validation studies examining indicators of suboptimal effort within the acute to sub-acute phase of mTBI are required.

Studies 2 and 3 shared some of the methodological issues identified as problematic in the studies reviewed in Study 1. The cross-sectional design prevented insights into causal relationships or underlying mechanisms. The direction of causation between psychological factors and cognitive functioning, or whether a third spurious variable exists, remains unknown. The absence of a traumatically non-brain injured control group also precluded inferences regarding potential interactions between the presence of mTBI and the observed relationships (Dikmen & Levin, 1993; Larrabee, Binder, Rohling, & Ploetz, 2013). The current conclusions are therefore limited to effects within mTBI patients. Additionally, the study did not control for the effects of litigation which may have impacted the results.

Implications. These empirical investigations highlight the possibility that acute post-traumatic stress, depression, and pain may be associated with cognitive performance in the acute to sub-acute phase of mTBI. Unexpectedly, the results suggest that acute post-traumatic stress, depression, and pain may each be associated with higher and/or lower cognitive performance following mTBI. These results highlight the need to consider these factors in the neuropsychological assessment of mTBI patients in clinical and research settings. Given the potentially contrasting associations among acute post-traumatic stress, depression, pain, and cognitive performance, and the high comorbidity of anxiety, depression, and pain (Bryant et al., 2010; Harvey & Bryant, 1998; Jamora et al., 2013), the interpretation of the neuropsychological test results of mTBI patients may be difficult. For example, while acute post-traumatic stress and depression were observed to be highly comorbid in the current sample, they were each associated with contrasting relationships with accuracy. Thus, these

relationships may mask each other in the manifest neuropsychological performance of mTBI patients.

Future Research

Future studies are required to replicate and extend the current findings. Large prospective longitudinal studies of consecutive trauma patients will be important to enable sufficient statistical power and generalizability (Carroll et al., 2004; Dikmen & Levin, 1993) and investigate causal mechanisms. Including traumatically non-brain injured controls is necessary to control for pre-existing factors and determine whether relationships among psychological distress, pain, and cognitive functioning are specific to mTBI (Dikmen & Levin, 1993; Larrabee et al., 2013). Further research will be important to determine the practical significance of the associations of psychological distress and pain with cognitive outcome, particularly in the context of other determinants of mTBI outcome.

As suggested by the results of the current research, it is possible that the relationships of psychological distress and pain with cognition following mTBI differ according to the severity of distress or pain. The use of structured clinical interviews as well as self-report questionnaires may be useful to explore distress at varying levels of severity. The use of a multidimensional measure of pain (e.g., the McGill Pain Questionnaire; Melzack, 1975; Melzack, 1987) may also provide a richer understanding of the association between pain and cognition in mTBI patients. Future research may benefit from considering the potential overlap in the measured psychological and cognitive constructs. The current research suggests that attentional tasks and cognitive measures that incorporate increased levels of demands (e.g., dual-tasks or extended durations) may confer the greatest sensitivity in detecting associations with distress and pain. Further investigation may also clarify the relationships among subjective experiences of mental effort, motivational factors, psychological distress, pain, and objective measures of cognitive performance.

Whether the relationships suggested by the current results are maintained beyond the acute to sub-acute period of recovery is a question for future research. Although one study found that depressive symptoms among mTBI trauma patients were associated with lower cognitive performance in a number of domains at 6 months post-injury, the analyses did not control for the effects of comorbid anxiety or pain (Ghaffar et al., 2006).

Conclusions

Psychological distress and pain appear to be associated with cognitive functioning in the acute to sub-acute period following mTBI. While a systematic review of the existing evidence suggests that psychological distress, particularly depressive symptoms, may be associated with lower cognitive functioning following mTBI, the current empirical investigations suggest that there may be complex relationships of psychological distress and pain to cognitive performance. Unidirectional relationships among psychological distress, pain, and cognitive performance following mTBI may be insufficient to fully characterize these associations. Attentional tasks or measures that incorporate increasing levels of cognitive demand may prove the most sensitive in detecting these relationships. Acute post-traumatic stress, depression, and pain may be important to consider in the interpretation of neuropsychological test results of mTBI patients. The comorbidity of psychological distress and pain, however, may complicate how these relationships manifest in the neuropsychological test results of mTBI patients.

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Appendix D

NSW GOVERNMENT | **Health**
Western Sydney
Local Health Network

HREC Committee Secretariat:

Professor Stephen Leeder AO
Chair
Professor of Public Health &
Community Medicine

Dr Jim Hazel
Secretary
Medical Graduate -
Endocrinologist

HREC Committee Members:

Sr Patricia Bolster RSM
Catholic Chaplain

Ms Therese Burke
Clinical Trial Coordinator

Mrs Patricia Fa
Clinical Trials Pharmacist

Mr John Fisher
Lawyer

Ms Jillian Gwynne Lewis
Patient Representative

Dr Anthony Harris
Medical Graduate – Psychiatrist

Ms Sheila Holcombe
CEO GP Network

Ms Jan Kang
Diversity Health Institute

A/Prof Ian Kerridge
Haematologist and Bioethicist

Rev Sarah Plummer
Minister of Religion

Mr John Shaw
Layman

Dr Geoff Shead
Medical Graduate - Surgeon

Dr Howard Smith
Medical Graduate – Endocrinologist

Prof Shih-chang (Ming) Wang
Medical Graduate - Radiologist

Ms Shane Waterton
Laywoman

Ms Christine Wearne
Clinical Psychologist

Our Ref: **HREC2010/11/4.8(3225) AU RED HREC/10/WMEAD/207**

17 February 2011

COPY

Dr Jennifer Chapman
Department of Rehabilitation Medicine
Westmead Hospital

Dear Dr Chapman

Project title: 'The effect of psychological distress on cognitive outcome following mild traumatic brain injury'

Receipt is acknowledged of Dr Jennifer Batchelor's letter dated 17 January 2011 addressing the matters raised in the Western Sydney Local Health Network HREC's letter dated 7 December 2010 following single ethical review of the above project at its meeting held on 30 November 2010.

This HREC has been accredited by the NSW Department of Health as a lead HREC to provide the single ethical and scientific review of proposals to conduct research within the NSW public health system. This lead HREC is constituted and operates in accordance with the National Health and Medical Research Council's *National Statement on Ethical Conduct in Human Research* and the *CPMP/ICH Note for Guidance on Good Clinical Practice*.

I am pleased to advise that the HREC has now granted ethical approval of this **single site** research project to be conducted at Westmead Hospital – Chief Investigator Dr Jennifer Chapman.

The following documentation has been reviewed and approved by the HREC:
- NEAF submission code AU/1/3D67010
- Protocol Version 01 dated 11 October 2010
- Revised Participant Information and Consent Form (Main Study) Version 02 dated 17 January 2011
- Revised Participant Information and Consent Form (for Follow-Up Contact) Version 01 dated 17 January 2011
- Clinical Interview Initial Assessment Version 01 dated 8 October 2010
- Clinical Interview 5 week Assessment Version 01 dated 8 October 2010
- Clinical Interview 5 month Assessment Version 01 dated 8 October 2010
- Participant Questionnaires Initial Assessment Version 01 dated 8 October 2010
- Participant Questionnaires 5 week Assessment Version 01 dated 8 October 2010

HUMAN RESEARCH ETHICS COMMITTEE (Westmead Campus)
Research Office, Room 2020 Clinical Sciences
Westmead Hospital, Hawkesbury Road, Westmead NSW 2145

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- Participant Questionnaires 5 month Assessment Version 01 dated 8 October 2010
- Neuropsychological Assessment Materials Initial Assessment Version 01 dated 8 October 2010
- Neuropsychological Assessment Materials 5 month Assessment Version 01 dated 8 October 2010

Please note the following conditions of approval:

- The Chief Investigator will immediately report anything which might warrant review of ethical approval of the project in the specified format, including unforeseen events that might affect continued ethical acceptability of the project.
- The Chief Investigator will immediately report any protocol deviation / violation, together with details of the procedure put in place to ensure the deviation / violation does not recur.
- Proposed amendments to the research protocol or conduct of the research which may affect the ethical acceptability of the project, must be provided to the HREC to review in the specific format. Copies of all proposed changes must also be provided to the relevant research governance officer.
- The HREC must be notified, giving reasons, if the project is discontinued at a site before the expected date of completion.
- The Chief Investigator must provide an annual report to the HREC and a final report at completion of the study, in the specified format. HREC approval is valid for 12 months from the date of final approval and continuation of the HREC approval beyond the initial 12 month approval period is contingent upon submission of an annual report each year. A copy of the Annual / Final Research Report Form can be obtained electronically from the Research Office on request.
- It should be noted that compliance with the ethical guidelines is entirely the responsibility of the Chief Investigator.

You are reminded that this letter constitutes *ethical approval only*. You must not commence this research project at this site until separate authorisation from the Chief Executive or delegate of that site has been obtained. Copies of this letter, together with any approved documents as enumerated above, must be submitted to the Research Governance Officer.

Should you have any queries about the HREC's Terms of Reference, Standard Operating Procedures or membership, please contact the HREC Executive Officer through the Research Office on 9845 8183 or emailing researchoffice@swahs.health.nsw.gov.au.
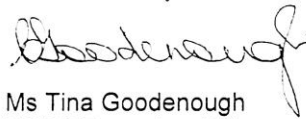
In all future correspondence concerning this study, please quote approval number *HREC2010/11/4.8(3225) AU RED HREC/10/WMEAD/207.*

The HREC wishes you every success in your research.

Yours sincerely

Ms Tina Goodenough
HREC Executive Officer
WSLHN Human Research Ethics Committee

cc   Dr Jennifer Batchelor, Department of Psychology, Macquarie University
       Miss Jessica Massey, Department of Psychology, Macquarie University

External Approval Noted- Batchelor (5201100172)

3 messages

Ethics Secretariat <ethics.secretariat@mq.edu.au> Thu, Feb 24, 2011 at 11:51 AM
To: Dr Jennifer Batchelor <jennifer.batchelor@mq.edu.au>
Cc: Miss Jessica Massey <Jessica.massey@mq.edu.au>

Dear Dr Batchelor

Re: "The effect of psychological distress on cognitive outcome following
mild traumatic brain injury"

The above application was considered by the Executive of the Human Research
Ethics Committee. In accordance with section 5.5 of the National Statement
on Ethical Conduct in Human Research (2007) the Executive noted the final
approval from the Sydney West Area Health Service and your right to
proceed under their authority.

Please do not hesitate to contact the Ethics Secretariat if you have any
questions or concerns.

Please do not hesitate to contact the Ethics Secretariat at the address
below, if you require a hard copy letter of the above notification.

Please retain a copy of this email as this is your official notification of
external approval being noted.

Yours sincerely

Dr Karolyn White
Director of Research Ethics
Chair, Human Research Ethics Committee