Neurocognitive Assessment of mTBI

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Abstract

The effects of Mild Traumatic Brain Injury (mTBI) typically resolve within days or weeks. However, a significant group of patients can report Persistent Concussional Symptoms (PCS). They may report a range of symptoms weeks, months and years post-injury. This review presents an overview of the pathogenesis, diagnosis and treatment options for mTBI and PCS, in adults and children. At early phases, post-injury, there are associations between neurological signs and symptoms, and neuropsychological functions and self-reported symptoms. However, over time, such associations become less coherent, and psychological issues become particularly relevant. Post-traumatic stress factors appear particularly important. We provide a biopsychosocial framework within which factors that predict such symptoms can be understood. An accurate diagnosis is critical for appropriate management of symptoms at various points post-injury.

Keywords

mTBI • Mild traumatic brain injury • PCS—post-concussional syndrome • PTSD—post-traumatic stress disorder • Biopsychosocial framework • Neuropsychology

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Introduction

Mild traumatic brain injury (mTBI) is a major public health issue globally. Around 80% of all TBIs are mild in nature and can be a major cause of disability leading to cognitive, mood and behavioural disorders (Fleminger and Ponsford 2005). For most people, injured symptoms usually resolve within days or weeks. Yet some argue that between 5 and 20% of those injured may be expected to have some ongoing problems—persistent Post-Concussional Syndrome (PCS)—weeks or months later (Kraus and Chu 2005;

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Ruff and Weyer Jamora 2009). The provenance of such ongoing problems is controversial. Indeed, a formulation of a survivor's "current status" post-injury is a challenge as there is a lack of clarity as to whether certain signs, symptoms and cognitive functions are reliable post-concussion sequelae (see Williams et al. 2010). Neurological symptoms and signs and associated neurocognitive dysfunction are key indicators of injury severity and subsequent recovery trajectory. We provide an overview of assessment for neurocognitive functions in mTBI and later PCS, and consider the issues which may influence testing. We argue how the outcome post-mTBI must be seen as that determined by biopsychosocial factors, whereby there can be, at early phases, associations between neurological signs and symptoms, and neuropsychological functions and self-reports, but, over time, psychosocial issues become particularly relevant in explaining symptoms. An accurate diagnosis is crucial for appropriate management of symptoms at various points post-injury.

Definitions of mTBI and PCS

There are various terms used, often interchangeably, for the type of injury and subsequent forms of symptoms associated with mTBI and PCS. In this review, we use the term mTBI for the initial injury and PCS for persistent symptoms following such injury (over weeks, months and years). The immediate symptoms of mTBI/concussion include headache, dizziness and nausea as well as physical signs which may include unsteady gait, slurred speech, poor concentration and slowness when answering questions (McCrory et al. 2005). A loss of consciousness (LOC) (e.g. Glasgow Coma Scale (GCS) score of 13 or above) is considered a mild injury. However, amnesia, especially post-traumatic amnesia (PTA), has been proposed as either an additional or an alternative diagnostic criterion to LOC, in conjunction with confusion (Alexander 1995). Indeed, a recent study indicated that PTA was a more effective measure of severity of mTBI than GCS in the context of predicting behavioural outcomes at 6 months post-injury (Tellier et al. 2009). Even where there is an absence of PTA and/or LOC, neurocognitive abnormalities may be detected in the immediate aftermath of a suspected concussion (McCrea et al. 2002). The presence of such features and other concussion symptoms (e.g. diplopia) can be used to grade immediate "concussion" (see Cantu 1998; Colorado Medical Society 1991; American Academy of Neurology 1997).

For determining PCS, there are The International Classification of Diseases (ICD) section F07.2 (post-concussional syndrome) diagnostic criteria and The Diagnostic and Statistical Manual of the American Psychiatric Association (DSM-IV) research classification (e.g. Carroll et al. 2004a). There is significant agreement between the two sets of criteria for general symptoms (Boake et al. 2004). However, in DSM, objective cognitive impairment and disturbance in social or occupational functioning are required (McCauley et al. 2007). Furthermore, within the ICD-10 (WHO 1992) criteria, there is no point at which symptoms can be regarded as persistent while DSM-IV specifies 3 months.

Rates and Risks for Injury

The yearly incidence of TBI in western countries (e.g. the USA and the UK) is around 180–250 per 100,000 people (see Yates et al. 2006). As noted, the overwhelming majority of head injuries are mild with estimates ranging as high as 90% (McMillan 2001). Risk factors for injury are age (early childhood, males in adolescence and young adulthood and females in older age), urban dwelling and lower socio-economic level (see Yates et al. 2006). Major causes include road accidents, falls, sporting injury, assaults, etc., and the age-related aspects of these causes are well documented. In non-sporting injuries, alcohol and/or drug influence is a key factor (Kolakowsky-Hayner and Kreutzer 2001). In non-western areas, rates are likely to be very high (see Hyder et al. 2007). The global effect of TBIs as a disease—with various degrees of burden—is argued to be highly underestimated and to be likely to increase substantially in the future (Hyder et al. 2007).

Consequences of mTBI/PCS

mTBI is "classically defined as an essentially reversible syndrome without detectable pathology" (Ommaya and Gennarelli 1974, p. 633). It is often noted that recovery following mTBI is rapid—with most acute symptoms resolving within hours, and then, typically, a person being symptom free by around 10 days (McCrea et al. 2003).

However, as noted above, an mTBI and/or concussion can be graded for severity and more complicated cases may be associated with differential outcomes—as we shall see, in particular, delayed recovery.

Typically, the more severe injuries occur from greater rotational acceleration–deceleration forces involved in the impact (Guskiewicz et al. 2000). Following impact, a neurometabolic cascade ensues (Giza and Hovda 2001). The short-term effects can include a lack of electro-chemical activity, haemorrhaging and axonal shearing, especially in the frontal temporal lobe area, although in mTBI these early deficits may largely resolve themselves (Lezak 2004). mTBI, therefore, tends to be characterised by the dysfunction and not destruction of neurons (Iverson 2005). Caution is, though, still warranted regarding signs of greater impact.

An indication of mTBI having long-term biological consequences was suggested in a population-based study of all people born in Denmark. In this study, it was shown that there was a two-fold increased risk of epilepsy after a mild brain injury (Christensen et al. 2009). However, there is lack of clarity on how such biological indicators are associated with outcomes. For example, serum markers of brain injury such as S100B (a calcium-binding protein) are thought to be useful for predicting initial acute severity of TBI, but it is argued that there is only a weak association between marker levels and concussion symptoms (see Bazarian et al. 2006). Indeed, it has been noted that normal levels of S-100B marker are helpful but abnormal levels tend not to predict the outcome (Iverson et al. 2006).

As noted, is possible that around 15% of those with mTBI may have ongoing problems (Ruff et al. 1996). In one study in Glasgow, the UK, 47% of young people and adults with mild head injuries experienced moderate to severe disability at 1 year post-injury (Thornhill et al. 2000). A further study in Glasgow of children with mTBI also showed high levels of disability—with 43% of the sample having problems 1 year post-injury (Limond et al. 2009). However, these participants, although noted as having a "mild" injury, may have had more "complicated" injury as they were typically hospitalized for observation for over a day. Other studies have found that neuro-behavioural sequelae are significant at over 2 years post-injury for TBI of milder severity. Hawley et al. (2004a, b) found that children with mild TBI were significantly more anxious compared to controls, and that behavioural and school-related problems were reported by families of mildly injured children as well as moderate and severely injured children at just over 2 years post-injury. As we explore further, below, there is some evidence that younger age at injury may be a risk factor for worse outcomes. However, factors accounting for this are not well explicated.

There is much debate, therefore, over whether persistent symptoms are "driven" by neurological or psychological factors, and what role there is for pre-morbid issues (Alexander 1995; Lishman 1988; Carroll et al. 2004b). As we shall explore, outcomes are highly variable across population groups studied (such as general patient groups versus those being monitored within sports), and in terms of whether there are links between actual physical injury and various symptoms and problems experienced later on.

Considerations Regarding Neurocognitive Testing

Neurocognitive functions are those abilities that are supposed to be present in certain areas of the brain for performing mental operations important for daily life. That is—key thinking skills linked to certain brain area. If the brain is affected, then these systems could be compromised. The following are key functions relevant to mTBI: executive functions—a set of cognitive abilities

that control and regulate volitional activities, such as planning, organising, self-awareness, impulse control and other self-regulatory functions; sustained attention—the ability to maintain consistent behavioural responses over time to specific stimuli during an ongoing repetitive task; divided attention—the ability to respond to two or more different tasks at the same time; and memory—the ability to encode, store and retrieve information within various time frames from the original encoding experience. There are two main reasons for neurocognitive assessment for concussion—to determine the presence of neurocognitive symptoms for early diagnosis of mTBI (in terms of severity and potential duration of injury) and to monitor recovery over days, weeks, months or even years later (Barth et al. 1989; Macciocchi et al. 1996; Davis et al. 2009). In the latter, there may be identification of lasting neurocognitive sequelae.

In the domain of testing for concussion symptoms, there are studies involving general patient group—typically those presenting to emergency departments (EDs)—and studies of particular risk groups—usually those involved in contact sports. There are also, increasingly, studies of military personnel—who are at particular risk of injury (e.g. from bomb blasts; see Hoge et al. 2008).

Over the past 20 years, the area of sports concussion management has provided much of the research base for informing clinical assessment practice in mTBI. Systems developed in this arena are being generalised to other groups (e.g. military; (and see Veterans and Dept. of Defense 2009)). The guiding principle of such testing is to ensure that those injured are taken out of the "game" until they are free of concussion symptoms and are therefore "fit" to resume play. The neurocognitive assessment forms part of a general review conducted to assess for concussion. Typically, athletes are tested out of season (baseline) and are then re-tested if they suffer a concussion/mTBI. They are, therefore, their own controls, and a significant deterioration from baseline suggests that the concussion has led to neurocognitive dysfunction which is not resolved. Where there are no baselines, performance would be compared to a representative control group. The neurocognitive element of the review may, therefore, provide a straightforward "cleared" (i.e. not showing neurocognitive symptoms) to resume, but may also indicate problems (if, on repeat testing, they do not achieve their baseline performance). In such circumstances, a review is needed of the person's fitness to return to the activity, and possible counselling regarding paced return to play (see McCrory et al. 2009). It is important to note, though, that a recent study indicated a high level of concussed athletes returned to play prematurely under AAN and Prague return-to-play guidelines (Yard and Comstock 2009).

Testing needs to be specific, sensitive, reliable and valid for identifying mTBI/PCS (Iverson et al. 2005). Validity is the accuracy of the measurement or the extent to which the test is measuring what it is purported to be measuring. Sensitivity and specificity refer to the likelihood of identifying either genuine positives or negatives, respectively. Sensitivity is the probability that someone in the category of interest (in this case, mTBI) is identified by the test. Conversely, if a test has a high level of specificity, it will reliably predict those who do have the condition versus those who do not have the condition. Reliability refers to the consistency of the measurement or the extent to which the test provides approximately the same result on each occasion it is used under the same set of conditions with the same participants. Test–retest reliability is especially important with regard to the use of baseline testing in sport when diagnosing concussion following head injury. This can be estimated by comparing the results of a test on the same population carried out at different times—e.g. using a correlation coefficient. However, such repeat testing can lead to practice effects, whereby the participant performs better in subsequent tests due to having "learned" from the previous experience (Collie et al. 2003).

Where it is known that a test is vulnerable to practice effect, then Reliable Change Indices (RCI) can be used to calculate what improvement would be expected from a person from baseline to post-concussional testing, and what adjustment is needed to take account of such supposed

improvement (Hinton-Bayre and Geffen 2002). The RCI is calculated by use of a control group to establish the average change between tests and an additional correction is made for test variability and reliability using an error term which produces a standard score (*Z*). Furthermore, use of alternate versions of tasks can limit practice effects (Collie et al. 2001).

Neurocognitive Assessment: Development of Methodology

Recovery of neurocognitive functions following concussion has been extensively examined within the paradigm of "return-to-play" studies in sports (see Barth et al. 1989; Macciocchi et al. 1996; Echemendia et al. 2001). These studies allow for large-scale prospective, repeat, follow-up and retrospective analyses of athletes at risk of concussion. Typically, as we note above, there are baseline measures available for athletes which provide an individual benchmark for monitoring performance.

Initially, neuropsychological tests were "paper and pencil" tests that could take between 4 and 6 h to administer. This was because symptoms of concussion were considered highly variable and multiple tests were needed to identify possible cognitive deficits (Echemendia et al. 2001). As the focus of interest became refined, shorter versions of testing procedures were developed. These were found sensitive to the mild cognitive problems indicative of acute concussion—such as attention and complex memory (Barth et al. 1989; Macciocchi et al. 1996; Boll and Barth 1983; Hughes et al. 2004). Importantly, the tests were more effective than subjective reports in distinguishing between the injured and the non-injured at 48 h post-injury (e.g. Echemendia et al. 2001). The tasks frequently employed in "paper and pencil" testing include tests, such as Digit Span (Lezak 1995) which tests working memory with mental rotation, Speed of Comprehension and Language Processing (Lezak 1995) which tests general cognitive level and speed of processing, Trail-Making Tests A and B (Lezak 1995) which test sustained and divided attention, Stroop Color and Word (Lezak 1995) which tests executive skills (especially inhibition) and Symbol Digit Modalities Test (SDMT), a measure of visual-spatial and motor speed and accuracy (Smith 1982).

More recently, computerised tests have been developed which offer distinct advantages over conventional methods (e.g. Campbell et al. 1999). Computerised systems provide an accurate measurement of reaction times (RTs) for the high-level forms of cognitive functioning that tend to be compromised following a concussion (Pellman et al. 2004). Standardised presentation of stimuli or random presentations of a large number of alternate forms provide improved test–retest reliability (Schatz and Browndyke 2002). Various packages have been developed including Immediate Post-Concussion Assessment and Cognitive Testing (ImPACT) (Maroon et al. 2000), a computerised neuropsychological test battery designed to measure a range of cognitive functions including attention and processing speed. Other software packages designed to be used to diagnose post-concussional cognitive deficits in sports include HeadMinder™ (see Erlanger et al. 1999) and CogSport™ (Cogstate 1999). CogState Sport™ measures simple and complex attention, reaction times and accuracy, as well as memory and problem solving ability (Schatz and Zillmer 2003) to create a composite score. This score then determines pass or failure (caution versus good/all clear). The tasks involve single playing cards or playing cards presented in multiples.

Computerised testing is also less vulnerable to practice effects compared to traditional testing, although such effects have been shown for these types of systems if tests are serially repeated on the same day on a normal population (see Collie et al. 2003). However, the main effect for practice occurs within the first few repetitions of the tasks, and then performance tends to become more stable (i.e. reaches a plateau) thereafter (Falletti et al. 2006).

Two of the other key advantages of computerised testing are with regard to practical and logistical limitations. Administration of traditional

neuropsychological tests requires one-to-one supervision as well as interpretation by a qualified person. In contrast, computerised testing can be carried out with less immediate supervision, remotely, and with individuals and groups simultaneously. We note, though, that testing processes may be undertaken by technicians but that this ideally should be under the supervision and/or guidance of an appropriately qualified psychologist—typically a clinical neuropsychologist. Indeed, interpretation of test results should preferably be carried out by a clinical neuropsychologist, although this may vary from country to country depending upon differing levels of training and availability (Echemendia et al. 2009). This is particularly important as such automated procedures may lead to the assumption that the computer can diagnose concussion and that those carrying out clinical evaluations may adopt a passive rather than an active role (Schatz and Putz 2006). It is important, in testing, to be aware of and take account of a range of factors that may influence testing (Schatz and Putz 2006) and that, as we have noted, test results are only part of the overall "data set" for formulating a clinical picture of an individual's functioning. Computerised tests may also lack some of the breadth and flexibility possible using traditional testing methods (Gualtieri and Johnson 2008). Consequently, while computerised testing may be increasingly used, traditional methods continue to have an important role to play, especially in a more individualised setting.

It is also worth noting that, while computerised testing is becoming available across a host of platforms for delivery, the use of technology may be lesser or greater among different groups within a society (Russell et al. 2003). Therefore, the attitude of the person being tested towards technology, especially if apprehensive, may lead to a poorer performance.

Iverson et al. (2005) examined the construct validity of ImPACT™ with the SDMT (Smith 1982). They found that the SDMT correlated most highly with the Processing Speed and Reaction Time composites from ImPACT™ suggesting that both tests are measuring a similar underlying construct. CogSport™ has been evaluated on 300 professional Australian football players as well as hundreds of healthy controls across a wide range of ages (Makdissi et al. 2001).

The Use of "Self-Rating" Scales in Assessment

Important information for assessment of mTBI/PCS would be gained from subjective accounts of patients/participants. We shall discuss later particular issues to be aware of that may influence reporting of symptoms. One of the main methods of gaining information, relevant to testing, is that of the use of standardised scales.

There is a range of scales available for assessment of mTBI/PCS (see Alla et al. 2009 for a review of those used in acute assessment sports). Some are "embedded" within neurocognitive testing systems (e.g. within ImPACT™, there is a 22-item scale), and there are "stand-alone" scales, such as the Rivermead PCS Questionnaire (see King et al. 1995). These scales typically contain items that address somatic, affective and cognitive symptoms. The structure of symptoms in mTBI/PCS in cognitive, emotional and physical domains is relatively consistent across a variety of studies using different questionnaires and in different populations, whereby symptoms are separate but are also associated (Potter et al. 2006). That is, there can be a "single-factor solution" (i.e. one consistent overall score) but analysis can also be undertaken of sub-groups of symptoms (Lannsjö et al. 2009). However, there is considerable consistency in symptom reporting across a range of PCS checklists and questionnaires—that is—they seem to be measuring the same underlying phenomena (Alla et al. 2009).

Although PCS has typically been associated with mTBI, individuals with moderate and severe TBIs can experience similar difficulties (e.g. Oddy et al. 1985). Also an analogous constellation of symptoms have been shown in non-brain-injured trauma controls (e.g. Meares et al. 2008; McLean et al. 2009): for example, in one prospective study, while 58% of people with mTBI met the criteria for PCS at 1 month post-injury, so did 34% of

orthopaedic controls (Bazarian et al. 1999). Overlap of symptoms with other clinical populations is also considerable, including individuals with depression (e.g. Iverson and Lange 2003), chronic pain (Smith-Seemiller et al. 2003) and chronic whiplash symptoms (Haldorsen et al. 2003). And subjective cognitive difficulties within those with mTBI/PCS may—in turn—be associated with comorbid anxiety, depression and fatigue (Stulemeijer et al. 2008).

It is important to note, though, that group differences may emerge with mTBI/PCS individuals compared to others. It has been found that mTBI individuals, for example, report higher levels of subjective cognitive difficulties compared to individuals with chronic pain (Smith-Seemiller et al. 2003) or orthopaedic controls (Gerber and Schraa 1995). The presence and severity of symptoms on such measures are not trivial due to their association with quality of life (e.g. Stålnacke 2007) and return to work (e.g. Nolin and Heroux 2006). Therefore, assessment of the severity and impact of symptoms (rather than their presence or absence) using scales such as the Rivermead PCS is indicated.

Neuropsychological Functions Post-mTBI

Sports Studies

There are many sports "return-to-play" studies that show that a single concussive episode may have little lasting neurocognitive consequence (Wall et al. 2006; and see Williams et al. in press). A meta-analytic review of neuropsychological testing of concussion in sports by Belanger and Vanderploeg (2005) identified 21 of 69 studies between 1970 and 2004 (key inclusion criteria including a control or baseline comparison). They reported mild-to-moderate effect of concussion in the first 24 h on global measures and larger deficits on memory (acquisition and delayed). However, there was, typically, full resolution by 7–10 days post-injury. They did note, however, that practice effects—particularly in the context of "comparison to baseline" studies—may be linked to an underestimate of concussion effects. Also studies in which prior head injury cases were excluded had smaller effect sizes than those that had not excluded such athletes. These findings suggest that prior "head injury" may be associated with greater cognitive sequelae. McCrea et al. (2003) followed up a concussed group ($n=94$) and an uninjured control group ($n=56$) of American college football players selected from a cohort of 1,631. They were tested at pre-season, then immediately after injury, at 3 h post-injury, and then again at 1, 2, 3, 5, 7, and 90 days post-injury. By 7 days, basic assessment on the SAC showed no significant group effect between a non-concussed and concussed group. Mild impairments in cognitive processing speed and verbal memory were noted for the concussed athletes at 2 and 7 days post-injury, and verbal fluency was still affected in the concussed group at 7 and 90 days post-injury. There was no evidence of other "lingering symptoms" at 90 days. Also, importantly, they noted that 10% of players needed more than a week for symptoms to resolve.

Studies using computerised systems have shown similar significant recovery trajectory, but also variation in outcome. Iverson et al. (2006) followed up concussed athletes ($n=30$) from baseline at 1–2 days, 3–7 days and 1–3 weeks post-injury using the ImPACT™. The athletes' scores on a range of measures (memory, speed, reaction time) were significantly reduced at day 1. Significant improvements had occurred by 5 days post-injury, although at 10 days post-injury, 37% of athletes had two or more composite scores that were lower than those of pre-season. Pre-existing head injury or presence of headaches (possibly indicating more complicated initial injury) was suggested as associated with compromised recovery. Collins et al. (1999) also found, in a sample of 393 American Football players, that a history of multiple concussions was associated with lowered neurocognitive performance in divided attention and visuo-motor speed.

Traditional neuropsychological testing has provided further support for the cumulative effects of concussion. Wall et al. (2006) showed that jockeys with repeated "historical" (more than 3 months since) concussions were less efficient

on tasks of executive functions and attention compared to those with a single concussion. Younger age accounted for much of the variance in decrement in attention, suggesting that younger age of injury, or repeat injury within a shorter time span, may be an important consideration. Other studies have not shown that repeat injury leads to cumulative effects on neurocognitive performance (Collie et al. 2006). A recent meta-analysis—which identified 10 relevant studies from 123 between 1970 and 2009—by Belanger et al. (2010) indicated that two or more mTBIs had "little overall association with cognitive performance several months later, although there is a small association with poorer performance on delayed memory and executive measures" (p. 5). They note, though, that the clinical significance of these effects was unclear.

The effects of repeat concussion, therefore, remain unclear (see Williams et al. 2010). Recent guidance on management of sports concussion notes "modifiers" that may be associated with worse outcomes (or delayed recovery), such as prior concussion, especially where the injuries have occurred within a short timescale, greater-than-1 min LOC, longer duration and severity of initial symptoms, as well as the greater amount of symptoms, concussive convulsions, younger age, presence of other conditions such as depression, a high level of risk associated with the sport as well as risky behaviour within the sport and finally use of medications such as psychoactive drugs or anticoagulants (McCrory et al. 2009).

Comparisons Between Sports and Patient Groups

There are key differences between sports populations and general patient groups. There may not, therefore, be direct comparators to patient populations. Sports people may "downplay" symptoms and have a strong motivation to return to play (Ruff and Weyer Jamora 2009). Also, athletes who are at risk may well be assessed as being concussed for relatively minor disturbances in consciousness within protocols in place for safety in sports. In patient groups, there is much greater heterogeneity of issues to consider: range of pre-morbid factors (educational, socio-economic, etc.), injury variables (mechanisms, forces, etc.) and degree of support available. A major difference between sports and general populations is that, in the latter, there are typically no baseline measures available. Therefore, the interpretation of test scores is based on the normative data provided by publishers—which inherently lowers sensitivity and specificity of injury detection.

Patient Studies

One early, well-controlled patient study—comparing 22 participants with mTBI versus 19 uninjured matched controls—revealed that single minor head injury was associated with mild but "probably clinically non-significant difficulties at 1 month after injury" (Dikmen et al. 1986). This applies especially to those without any compromising pre-existing conditions. Neurocognitive problems included problems with concentration and new learning, but these were not present at 1 year post-injury.

A meta-analytic review of neurocognitive studies (from 1970 to 2004) of patients with mTBI by Belanger and Vanderploeg (2005) identified 39 of 133 studies that met the key criteria (participants sought medical attention and there was grading of severity of injury). Of eight cognitive domains assessed in "selected" samples, problems were mostly confined to verbal fluency (executive skills) and delayed memory. In those who were "unselected", there was no difference to controls at 90 days post-injury, although litigation appeared to be a moderating factor. Another meta-analysis by Schretlen and Shapiro (2003) indicated that cognitive performance of mTBI patients could not be distinguished from matched controls at 1 month post-injury. Such trends lend support to the notion that recovery tends to be "complete" by 3 months (see Binder 1997; also see Frencham et al. 2005). Pertab et al. (2009) noted caution though, as it may be that lasting neurocognitive deficits can be found within sub-sets of neuropsychological

measures—suggesting that some participants may have ongoing neurocognitive sequelae.

How early "complicating" factors relate to neuropsychological functions has been recently explored. Shreedy et al. (2006) investigated prediction of post-concussion symptoms using an ED assessment that examined neuropsychological and balance deficits and pain severity of 29 concussed individuals. Thirty participants with minor orthopaedic injuries and 30 ED visitors were recruited as control subjects. Concussed and orthopaedically injured participants were followed up by telephone at 1 month to assess symptom severity. In the ED, concussed subjects performed worse on some neuropsychological tests and had impaired balance compared to controls. They also reported significantly more post-concussive symptoms at follow-up. Neurocognitive impairment, pain and balance deficits were all significantly correlated with severity of post-concussion symptoms. The findings suggest that a combination of variables assessable in the ED may be useful in predicting which individuals will suffer persistent post-concussion problems. Brief short-form traditional assessments have continued to be studied in the literature. Shores et al. (2008) examined whether administering the Revised Westmead Post-traumatic Amnesia (PTA) Scale (R-WPTAS) in addition to the GCS would increase diagnostic accuracy in the early identification of cognitive impairment in patients with mTBI. Data were collected from 82 consecutive participants with mTBI who presented to the ED of a level-one trauma centre in Australia. A matched sample of 88 control participants who attended the ED for reasons other than head trauma was also assessed. All patients were assessed using the GCS, R-WPTAS and a battery of neuropsychological tests. Patients with mTBI scored poorly compared with control patients on all measures. The R-WPTAS showed greater concurrent validity with the neuropsychological measures than the GCS and significantly increased prediction of patients with mTBI who had cognitive impairment. The R-WPTAS also significantly improved diagnostic accuracy in identifying patients with mTBI who may have PTA. Administration took less than 1 min, and since early identification of a patient's cognitive status facilitates management decisions, it was recommended for routine use whenever the GCS is used.

The emerging literature on recovery in childhood will be discussed in greater detail below. However, for now, we wish to note that for children recovery is complex and tends not to be characterised by problems with neurocognitive functioning per se but rather with neuro-behavioural difficulties. Indeed, Hawley et al. (2004a, b) showed that for those injured between 5 and 15 years, with a mean of 2.2 years post-injury, there was no evidence to suggest a threshold of injury below which the risk of late sequelae could be safely discounted, although the risks increase with severity.

Relationships Between Neurological and Neurocognitive Functions

Whether mTBI leads to reliable changes in cognitive status associated with particular forms of injury (severity, location, etc.) is addressed in studies, where neuroradiological and neurocognitive data can be linked. There is emerging evidence linking neurocognitive dysfunction to neuro-imaging findings post-mTBI. We shall now review the strength of such relationships. A study of a group of patients with "day-of-injury" CT scans showing "abnormalities" (hence "complicated"), compared to uncomplicated, showed that complicated mTBI was associated with worse performance for executive and attention functions. A further study of 20 complicated mTBI (based on GCS falling between 13 and 15 and/or CT scan results) and "uncomplicated" matched patients revealed that the complicated mTBI patients performed worse on memory tasks (visual reproduction and verbal learning) (Lange et al. 2009). MRI scanning provides for more "fine-grained" imagery of brain systems. An MRI study of neuropsychological functions in 30 mTBI patients compared to matched controls indicated that patients with traumatic lesions performed more poorly on neurocognitive tasks within 4 days of injury compared to those with non-specific lesions or no lesions (Kurca et al. 2006).

Performance was worse for concentration and attention.

It appears that neurocognitive recovery follows a variable time course. A study by Hughes et al. (2004) revealed that patients identified as complicated by MRI were also found to have neuropsychological dysfunction, with memory, attention and executive functions being impaired. Interestingly, however, there was no difference in terms of whether those with normal or abnormal scans returned to work or not. A recent study by Kwok et al. (2008) of "complicated" patients (abnormal CT scan within 24 h of injury) at 1 and 3 months post-injury compared to non-patient controls indicated that the complicated group were poor on speed, attention (both sustained and divided) and executive functions at the time of 1 month, but, by 3 months, speed and divided attention were much improved. Sustained attention and executive functions were not fully resolved, however. In a similar study by Hofman et al. (2001), further evidence of coherence between neurological functions and neurocognition over time has been found. In their MRI with single-photon emission CT (SPECT) study, it was found that 57 and 61% of their 21 and 18 patients (GCS on average 14.48) had abnormalities on MRI and SPECT imaging, respectively, within 5 days after injury. Moreover, there was associated brain atrophy at 6 months[63]. Those with complicated mTBI were slower on reaction time tasks.

Functional imaging studies have provided further evidence of systems implicated in mTBI. In an fMRI study of 18 mTBI patients up to 1 month post-injury, there were significant changes in activation patterns (McAllister et al. 2001). The patient group, compared to controls, had differential activation patterns—in bilateral frontal and parietal areas—on working memory tasks under moderate load. An fMRI study of working memory task with concussed athletes (15 "symptomatic" participants who had sustained their last injury from 1 to 14 months previously) revealed differential activity patterns compared to a control group (Chen et al. 2004). They had weaker activity in areas related to self-monitoring—such as prefrontal cortex. Chen and colleagues conducted fMRI imaging for working memory task on athletes 1 month post-injury who had self-rated for severity of symptoms—(a "low" ($n=9$) symptoms group and a "moderate" ($n=9$) symptoms group, and a control group). The moderate group showed less activation in the ROI identified in controls for the tasks—the dorsolateral prefrontal cortex. Both concussed groups had increased activation in the left temporal area (Chen et al. 2007). These findings suggest that it may be possible to detect physiological changes in neurological systems linked to changes in cognitive functions.

Associations between neurological activation and cognition have recently been investigated with transcranial magnetic stimulation (TMS) and electroencephalogram (EEG) over a 30-year period. In this study, 19 former athletes who had sustained concussions 30 years prior to testing were compared to 21 healthy, uninjured athletes. The concussed group performed poorer on tasks of memory and response inhibition (that is, stopping oneself from doing something). Also, athletes with a history of concussion showed significant P3a latency delays and amplitude reductions compared to controls. The duration of the Cortical Silent Period (CSP) on TMS was also reported to be significantly longer in the concussed group—which may indicate change in motor cortical excitability (De Beaumont et al. 2009).

Such studies, therefore, indicate that "complicated" mTBI may be predicted on the basis of neurologic evidence and tracked by neurocognitive testing. However, there are important limitations that relate to a number of these studies. First, across most studies, there is insufficient information as to whether those who display any abnormality or differential activation pattern may have had pre-morbid factors relevant to such functions. It is known, for example, that ADHD may be a risk factor for early head injury (Keenan et al. 2008). Second, particularly at long term post-injury, there is a possibility that participants were inaccurate in their reports on the severity and number of mTBIs. Third, numbers of participants tend to be low, and retention rates low, which leads to concerns over the representativeness of the groups studied.

There are also contrasting findings. A 1-year prospective study in Norway of 115 patients with Mild, Moderate and Severe TBI found that the Mild group reported greater PCS symptoms at 3 months but not at 1 year post-injury (Sigurdardottir et al. 2009). Also, at 3 months—there was no difference in the Mild group between those meeting the PCS criteria on the basis of any inter-cranial pathology—detected by MRI.

Psychological Processes Mediating Outcomes

Persistence of symptoms may, then, be due to residual neurological injury. However, given the lack of consistent association among neurological status, neurocognitive function and self-reports, there is a clear role for consideration of a wider array of issues—particularly psychosocial—in the maintenance, and, indeed possibly, genesis, of problems in the longer term. In this context, it is worth noting that, while factors such as female gender and previous psychiatric history (see Carroll et al. 2004a) have been linked to poorer outcome, much of the literature has been critiqued both conceptually and methodologically (see Carroll et al. 2004b), with failures to replicate significant findings being noted: limitations can include issues around consistency of mTBI definitions, unclear or heterogeneous populations, use of cross-sectional rather than longitudinal study designs and questions around potential recall and recruitment biases.

To provide a more comprehensive understanding of the roles of various biological, psychological and social factors in accounting for outcomes, diathesis-stressor models have been proposed. These combine both "organic" and "psychogenic" factors to account for PCS post-mTBI (Kay 1993; Alexander 1995; Jacobson 1995: King 2003; Wood 2004). Lishman (1988) provided an early version of this model by noting how early biological mechanisms may be responsible for initial PCS symptoms, but "vicious cycles" of psychological factors may be responsible for their persistence. King (2003) provided a model positing a number of potential "windows of vulnerability", such as early worries about symptom longevity and various coping styles which may influence symptoms. There have been recent advances in explicating psychological reactions to trauma that may have a significant role in PCS symptomology. Also, there has been evidence to show that patients may misattribute subjective phenomena as due to mTBI. For example, as we shall discuss below, mood symptoms associated with Post-traumatic Stress Disorder (PTSD) could be mistaken for PCS (Hoge et al. 2008).

Psychological Reaction

There are elevated rates of psychiatric co-morbidity in PCS groups (Ruff and Jurica 1999). This may be a response to persisting effects of brain injury on cognition and associated limitations in functioning but could be a psychological reaction to the trauma event. PTSD has recently been shown to develop post-TBI (e.g. King 1997; Bryant and Harvey 1999). It had been thought that a loss of memory for the event would be a protective factor for PTSD post-TBI. However, a number of studies have shown that PTSD does occur after mild, and even moderate to severe, TBI (see Williams et al. 2003). Potential mechanisms for such post-traumatic stress (PTS) have been identified—such as islands of memory, external causal attributions, etc. (see McMillan et al. 2003 for a review). Rates of PTSD after TBI vary hugely—from 0% prevalence through to 48% in one review (Harvey et al. 2003). Moreover, there has been ambiguous evidence as to whether amnesia may be a protective factor (Gil et al. 2005; Caspi et al. 2005; Bryant et al. 2009) or not (e.g. Greenspan et al. 2006). Very recently, a large-scale study of 920 trauma patients in Australia by Bryant and colleagues showed that mTBI patients were more likely to develop PTSD compared to non-TBI controls, but that longer PTA was a protective factor (Bryant et al. 2009).

In a recent retrospective review of the US soldiers returning from Iraq, post-concussional symptoms were elevated in individuals exposed to mTBI compared with other injuries, but PTSD

(along with depression) emerged as a major factor mediating the relationship between the two (Hoge et al. 2008). Belanger et al. (2010) also recently identified a role for PTSD in symptomology post-mTBI. In their study of mTBI and moderate to severe TBI patient groups ($n = 225$: 97% were active duty or veteran military personnel), those with mTBI endorsed more symptoms than the moderate to severe groups. However, when controlling for variance due to the effect of PTSD, the mTBI group was no longer different from the other groups (across all three domains of affective, somatic and cognitive domains). It is important to note, though, in this context, that the relationship between PTSD and PCS is complicated by overlapping domains and other methodological issues (Chalton and McMillan 2009). For example, it is questioned whether PTSD measures can be sensitive to the effects of non-traumatic stressors, and whether responses may reflect personality traits such as negative affectivity (Shapinsky et al. 2005). Questions, therefore, persist around PTSD and other psychiatric disorders, such as depression in relation to mTBI, their relationship with pre-injury psychiatric status and the extent to which they moderate or mediate the interaction between an injury and PCS. However, evolving stress (e.g. reactions to changed life situations and circumstances) and distress (including depression, as well as a potential range of anxiety disorders rather than PTSD exclusively) in the days, weeks and months after mTBI seem likely to be important factors in the formation and maintenance of PCS.

Attributions and Expectations

There are various ways in which subjective biases can influence reporting of symptoms, and even moderate test performance. Individuals with persistent PCS may under-report normal "post-concussional" symptoms they experienced prior to their head injury—the "Good Old Days" phenomena (Iverson et al. 2010). Even the act of reading vignettes related to head injury has been shown to lead to uninjured controls expecting post-concussional symptoms (Mittenberg et al. 1992). Suhr and Gunstad (2005) demonstrated the phenomena of how expectation can influence test performance. They administered neurocognitive measures (memory, attention and executive functioning) to two groups of undergraduates who had reported a history of mTBI. One group were made aware of their "head injury" and what kinds of cognitive effects occurred post-head injury prior to testing ("diagnosis threat" group). This group showed significantly worse performance on a number of neurocognitive measures. Whittaker and colleagues and others (e.g. Fenton et al. 1993; King et al. 1999; Meares et al. 2006) suggested that psychological mechanisms may play a role in influencing later symptoms early on after injury. They examined the extent to which perceptions of symptoms on the Revised Illness Perception Questionnaire (Moss-Morris et al. 2002) within the first 3 weeks after mTBI predicted the presence of persistent symptoms at 3 months after injury. They found that individuals who initially viewed their injury as having serious and persisting negative consequences had greater symptomology at 3 months.

Involvement in medico-legal or compensation claims may lead to expectations to be moderated (Binder and Rohling 1996; Carroll et al. 2004a) with the possibility of symptoms being maintained. Individuals being involved in tort as compared to no-fault insurance claims following motor vehicle incidents have been shown to be subject to slower recovery (Cassidy et al. 2004). Also, there is evidence that at least a proportion of individuals with persisting difficulties after mTBI can show evidence of at least suboptimal effort on formal neurocognitive assessment (Larrabee 2003; Mooney et al. 2005). However, it is also important to consider how involvement in a medico-legal action—with repeated rehearsal of symptoms and an emphasis on blame and culpability (see Lishman 1988; Jacobson 1995)—may play a role. And it is important to consider the roles that comorbid issues, such as anxiety and pain, have on cognitive performance (e.g. Radanov et al. 1999; Nicholson et al. 2001), for example by distracting attention form the "task in hand".

Children and Adolescents

With regard to children, the literature is relatively underdeveloped compared to that for adults with mTBI. As we have noted above, there is some evidence of problems in children post-mTBI. However, the evidence base is not strong, and there are methodological problems with a range of studies (see Carroll et al. 2004a, b), particularly with regard to lack of control groups and consideration of pre-morbid and non-injury factors. In general, as Carroll et al. (2004a, b) noted: "Where post-concussion symptoms are present, they are usually transient in nature". In their review of a wide range of studies, they note that there are often pre-morbid issues and poverty factors that are linked to worse outcomes (Carroll et al. 2004a, b). However, as also noted above, there have been some recent studies suggesting a higher level of disability than expected (Limond et al. 2009).

A study by Wrightson et al. (1995) provides interesting insights into how such problems may occur. They followed up pre-school children who had mTBI soon after injury and then at 6 months and a year. There was an orthopaedic control group. They found no differences after injury on a range of cognitive tasks. But, at 6 months and then at 1 year, the children with scored less well on tasks measuring visual problem solving. There was also an association with further injury. A prospective, longitudinal follow-up at 23 years post-injury study by Hessen and colleagues (Hessen et al. 2007) identified PTA as a particularly important factor in mTBI in childhood injuries. They tested 45 and 74 adults who had injuries 23 years previously as children or adults, respectively. Those who had injuries in childhood, and had a PTA of half an hour or more, were found to have vulnerability to chronic, mild, neuropsychological dysfunction. They note that here was no control group, but they had taken account of pre-injury factors in analysis. Cognitive outcomes, and the effect of advice giving, were investigated by Ponsford et al. (1999). They found that initial symptoms had resolved by 3 months, but children with previous "head injury" or learning difficulty had ongoing problems. On a related theme, cognitive reserve—a resilience issue—was examined in a study by Fay et al. (2009). They found that children with lower cognitive ability with complicated mTBI (determined by MRI) were especially prone to cognitive symptoms. The needs of children and families were addressed by Hawley (2003) who found that across severity of TBI there were significant problems associated with anxiety over time with no significant resolution of problems when comparing mTBI and moderate to severe TBI groups. Recent work by Anderson et al. (2009) provides an important heuristic for understanding these differential effects of childhood injuries (Anderson et al. 2005). They have referred to the need to consider the early vulnerability model of recovery from brain injury in childhood and suggest that age of injury and age at testing are important factors in the context of neuro-plasticity and crowding effects (see Anderson et al. 2009). Family functioning variables are also strong mediators of outcome both pre- and post-injury (Yeates and Taylor 2005) and these have to be considered as part of a wider biopsychosocial assessment protocol.

Tonks et al. (2011) have studied a range of mediating variables of recovery from various forms of Acquired Brain Injury in childhood—including age of injury, underlying cognitive factors and socio-emotional functioning. This work suggests that there are associations between hyperactive behaviour and speed of processing deficits in children between the ages of 8–10 years, and there are significant links between hyperactivity and difficulties in establishing peer relationships for children aged 10–15 years. In the samples used in these studies, some children had milder traumatic brain injuries, although we note that they may well not be fully representative of the majority of children mTBI due to selection biases. In general, this work points to the need to incorporate not only self-report and cognitive testing measures into assessment schedules but also to widen the pool of enquiry to psychosocial domains and consider additional more subtle executive assessment measures of social and emotional processing and inference (e.g. of another's "Theory of Mind"

(TOM) shown by expressions of emotion). In the child literature, assessments such as the Strengths and Difficulties Questionnaire (Goodman 1996) provide well-standardised reliable data on the child in both family and school settings with child, teacher and parent reporting options. It provides measurement for emotional symptoms, conduct problems, inattention, peer relationships and pro-social behaviour. Child versions of the measures such as The Awareness of Social Inference Test (TASIT) (McDonald et al. 2006) are not forthcoming at present, although Baron-Cohen et al. (1997) has routinely used similar measures with children with Autism Spectrum Disorder (ASD) to determine abilities such as Theory of Mind and empathy. The development and refinement of measures that are sensitive to mTBI groups would be important for children, who appear to develop subtle executive and higher level cognitive and socio-behavioural difficulties.

Summary and Conclusions

mTBI may be best seen as a spectrum disorder, with the "dosage" of injury setting a context for recovery and/or resolution of symptoms. Neurocognitive functions appear to recover rapidly early on. Studies linking radiographic neuroanatomic data and neurocognitive functions suggest functional changes in brain activation which may resolve readily but that there may be structural changes—particularly evident in "complicated" cases. In such cases, delayed recovery (at 3 months to a year) may be anticipated. There appears to be concordance between neurological findings and neurocognitive functions early after injury, but, with time, such associations dissipate. Subjective complaints also appear to become less "tied" to neurocognitive functions over time. The role of psychosocial factors in symptomology is coming under increased scrutiny, with such issues as PTSD and expectations being identified as influential in predicting outcomes. Compared to adults, assessment of children and adolescents is complicated by the dynamics of neurocognitive development and significant contextual factors. It is crucial, therefore, that assessments are undertaken not only to identify neurocognitive processing, but also such issues, with careful monitoring over return to activities. With a better understanding of the multiple causal variables that interplay in mTBI and PCS, patients and relatives may be given better advice to ensure that recovery is maximised.

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