Etiology of the post-concussion syndrome: Physiogenesis and psychogenesis revisited

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Abstract. In his seminal article, \textit{Physiogenesis and Psychogenesis in the 'Post-Concussional Syndrome,'} published over 20 years ago, Lishman\textsuperscript{53} proposed that neurobiological factors account for the development of the post-concussion syndrome and psychological factors become primarily responsible for maintaining it in the chronic phase. Over the 20 years that followed, researchers have advanced our understanding of the etiology of the post-concussion syndrome. Our review of this evidence suggests that neurobiological and psychological factors play a causal role in post-concussion symptoms from the outset, and thus, Lishman's causal model should be updated. If we can clinically identify individuals on a trajectory of poor recovery in the acute post-injury stage, then we can direct secondary prevention towards modifiable risk factors.

Keywords: Mild traumatic brain injury, etiology, rehabilitation

1. Introduction

Having persistent symptoms is an atypical but well-documented outcome from mild traumatic brain injury\textsuperscript{[38,41,46,57]}. These symptoms, including headache, fatigue, dizziness, and difficulty concentrating, can be associated with functional disability\textsuperscript{[55]}. The etiology of poor outcome from MTBI, typically referred to as post-concussion syndrome (PCS) or post-concussional disorder, has been debated for as long as this condition has been recognized. In his seminal article \textit{Physiogenesis and Psychogenesis in the 'Post-Concussional Syndrome,'} published over 20 years ago, Lishman\textsuperscript{[53]} proposed that "organic factors are chiefly relevant in the earlier stages, whereas long-continued symptoms are perpetuated by secondary neurotic developments" (p. 460). With regard to acute PCS symptoms, he wrote: "At the outset, these are firmly organic in origin" (p. 468). Then, "over the many weeks and months [following MTBI] there is a shifting balance" (p. 468), wherein neurobiological factors subside and psychological factors emerge to maintain PCS. Lishman noted that spontaneous neurobiological recovery occurs fairly rapidly in most people, but symptomatic and functional recovery could be hampered by psychological problems.

The central aim of this paper is to re-evaluate Lishman’s hypothesis in light of the accumulating evidence that psychological factors play an important etiological role from the outset. This refinement of the role for psychological factors is not merely academic. Identifying modifiable risk factors for poor outcome after MTBI is essential for secondary prevention, i.e., treatment aimed at preventing persistent symptoms and improving functional outcome. A systematic review of prognostic factors concluded that compensation-
seeking predicts poor outcome and that other possible predictors include age, injury mechanism, and pre-injury mental health [17]. Unfortunately, none of these risk factors are directly modifiable, and as such, they provide little guidance for acute management or secondary prevention. However, if early maladaptive psychological markers can be identified, they might represent viable treatment targets. This would prepare the way for advancements in the prevention of a condition that, once it reaches the chronic stage, has no evidence-based treatment [2,3].

Lishman’s model predicts that: (a) psychological distress minimally influences the acute presentation of PCS, (b) psychological distress increases over time in MTBI patients who do not recover, (c) the relationship between psychological distress and PCS symptoms strengthens over time, and (d) early psychological distress is a relatively weak prognostic indicator for long-term PCS. The research evidence relevant to these predictions is reviewed in turn. The reader should note that throughout this review we will use the acronym “PCS” to refer to the post-concussion syndrome (i.e., presence/absence of a cluster of symptoms in an individual) and “PCS symptoms” to refer to the severity and frequency of its features along a continuum.

2. Does psychological distress influence the acute presentation of PCS?

Within the first week after MTBI, prevalence estimates for emotional symptoms such as anxiety, depression, and irritability range from 4–5% [95] to 49–63% [21]. In prospective studies that include serial assessments, psychological distress is detectable at the time of study enrolment, even when done within hours of the injury [37]. Before being discharged from the hospital, 5–14% will meet criteria for Acute Stress Disorder (ASD) and an additional 5–19% will exhibit subthreshold ASD symptoms such as intrusive re-experiencing, hypervigilance, and avoidance of trauma-related stimuli [13,32]. Although emotional symptoms tend to be less common than somatic and cognitive symptoms such as headaches, fatigue, mental fogginess, and dizziness in the acute stage [54], early emotional symptoms occur across motor vehicle accident, sport, and military contexts. Thus, psychological distress is a part of the acute PCS picture for many patients.

Several studies have administered standardized measures of psychological functioning concurrently with PCS symptoms soon after MTBI. PCS symptom severity is consistently found to correlate with distress, more so than with measures of MTBI severity or neuropsychological test performance. For example, King [44] studied patients with mild to moderate TBI, based on post-traumatic amnesia duration of 0 to 44 hours (only 4% exceeded 24 hours). Participants were assessed 7–10 days after their injury. Anxiety and depression symptoms (as measured by the Hospital Anxiety and Depression scale) correlated strongly with concurrent PCS symptoms (r values = 0.60 to 0.65). Measures of intrusive thoughts about the injury event and efforts to avoid those thoughts (on the Impact of Events scale) correlated 0.69 and 0.60 with PCS symptoms, respectively. In contrast, neuropsychological measures were not significantly correlated with PCS symptoms (0.07 to 0.18). King et al. [45] replicated these findings with an independent sample, using very similar methodology.

Landre et al. [49] studied hospitalized patients with uncomplicated MTBI and polytrauma and compared them to trauma controls. Almost all (92%) of their MTBI patients had comorbid non-brain injuries requiring admission to a trauma unit. They were assessed 3.9 days (SD = 4.4) post injury. MTBI patients and trauma controls did not differ on PCS symptom reporting. In the full sample, PCS symptoms correlated more with emotional distress (r = 0.37 to 0.38) than with pain (r = 0.13 to 0.18). Neuropsychological performance was related to MTBI but not PCS symptoms.

Meares et al. [60] recruited consecutive cases with uncomplicated MTBI (i.e., cases with an intracranial abnormality on neuroimaging were excluded) who completed self-report psychological measures at an average of five days post injury (range = 1 to 12). Participants were grouped into presence/absence of PCS using ICD-10 criteria (3+ symptoms endorsed as being experienced “Often” or more; World Health Organization [94]). Forty-eight percent of their sample met these criteria, reporting an average of five PCS symptoms. Group differences on the psychological measures were large, with Cohen’s d effect sizes of 0.86 and 0.93 for anxiety and depressive symptoms, respectively. The dissociative cluster on the Acute Stress Disorder Scale best differentiated those MTBI cases with versus without PCS, with an effect size of 1.42. Of note, group differences in concurrently measured neuropsychological performance were comparatively small, with effect sizes from 0.02 to 0.48. The prevalence of prior MTBIs and demographic characteristics were comparable between the two groups.
Meares et al. [61] recruited a new sample of patients with uncomplicated MTBIs as well as trauma control subjects and had them complete a battery of measures within two weeks of their injury (average = five days). In a multivariate logistic regression analysis with PCS diagnosis as the dependent variable, injury type (MTBI vs. trauma control) was non-significant. That is, those with bodily injuries (44%) were just as likely to meet ICD-10 criteria for PCS as those with MTBIs (43%). In contrast, the significant predictors were: pre-injury psychiatric diagnosis (odds ratio = 5.76), female gender (OR = 3.33), estimated IQ (OR = 1.06), cognition measured by the Symbol Digit Modalities Test (OR = 0.93), and the Acute Stress Disorder Scale total score (OR = 1.06).

Lange et al. [50] studied four groups: MTBI, MTBI with depression, outpatients with depression, and healthy controls. The time post injury varied widely around the average of 52 days, but more than half were seen within the first month. The most PCS-like symptoms were reported by patients who had sustained an MTBI and had comorbid depression, followed by uninjured outpatients with depression, MTBI cases without depression, and healthy controls. The effect of having depression with MTBI on PCS symptoms was very large compared to MTBI alone (Cohen’s d = 1.4).

Snell et al. [82] recruited patients who sustained an MTBI, including those with intracranial neuroimaging abnormalities. They were seen initially at an average of 42 days post injury (range = 8 to 90). Poor outcome was defined as meeting the ICD-10 PCS symptom criteria as well as functional disability. Poor outcome was not associated with pre-injury psychiatric history or comorbid psychiatric diagnosis in this sample. The authors reported medium to large effect sizes on the Hospital Anxiety and Depression Scale (d = 0.6 and 1.0 for the anxiety and depression subscales, respectively) between participants with good and poor outcome at study entry. Measures of injury severity – Glasgow Coma Scale score, loss of consciousness duration, and post-traumatic amnesia duration – were not different between the good and poor outcome groups.

Taken together, the above-reviewed studies provide fairly strong evidence that early psychological distress is common after MTBI and related to concurrent PCS symptoms. It is important to point out that Lishman’s article describes an etiological model of the development of the PCS. In other words, he proposed that acute symptoms are largely caused by organic factors and chronic symptoms are largely caused by psychological factors. The aforementioned studies demonstrating a relationship between early psychological distress and PCS symptoms are relevant to our evaluation of Lishman’s hypothesis insofar as the former causes the latter. However, because all of the studies we reviewed in this section relied on correlational analyses, they are unable to establish this causal link.

One alternative explanation is that a third variable, MTBI, causes both emotional and PCS symptoms. Theoretically, initial neurometabolic changes in the brain could involve and include perturbations in endogenous neurotransmitter systems precipitating a depressive disorder. Moreover, altered brain physiology may make people less resilient and adaptable to personal and environmental stressors, which in combination precipitates the development of depression. Researchers have reported that people who sustain a TBI are at increased risk for developing depression [48,78]. However, the underlying cause(s) of depression following TBI of any severity, are complex and not well understood. There may also be neurobiological alteration of brain systems involved in stress reactions, but it is not clear whether this alteration is caused by MTBI pathophysiology, the experience of a stressful event, or both [30,58,66,74].

A challenge to this “third common-causal variable” explanation is that psychological factors present prior to the injury are among the strongest predictors of the severity and course of PCS. A history of pre-injury psychological problems [17,61], certain personality traits [28,76], and stressful life experiences [90] all appear to contribute.

Another challenge is that the severity of an MTBI does not appear to be strongly associated with either PCS or emotional symptoms. Many studies report minimal association between MTBI severity indices (such as loss of consciousness and post-traumatic amnesia) and acute or chronic PCS symptoms [17]. Moreover, acute PCS prevalence may be comparable in patients admitted with MTBI and trauma controls with no head injuries [61,62,72]. Similar findings have been reported in military samples. Fear et al. [26] noted that the rates of moderate-severe PCS-like symptoms after blast exposure (27%) during military service were similar to the rates of these symptoms associated with other factors (e.g., exposure to depleted uranium and/or assisting wounded soldiers = 32%). In another sample [35], symptom reporting was more common in soldiers who experienced a loss of consciousness or altered mental status compared to soldiers with other injury types, but this increased risk disappeared after controlling for PTSD and depression. Similarly, Polusny et al. [71] found that in-theatre PTSD was more predictive of...
post-deployment health outcomes than in-theatre MTBI exposure. If the causal link between MTBI and PCS symptoms is questionable, the link between MTBI and emotional symptoms must be even more so.

It is also conceivable that the distress-PCS association is an artefact of symptom overlap between PCS and comorbid psychiatric disorders. A cursory examination of the diagnostic criteria for Major Depressive Disorder, anxiety disorders, and PCS reveals considerable overlap. Symptoms such as fatigue, sleep disturbance, and concentration difficulties are core features of depression and the anxiety disorders. This confound, for example, might explain Stulemeijer et al.’s [86] finding that post-traumatic stress predicted poor outcome defined by symptom reporting but not employment status (return to work).

The psychological measures used in most of the studies reviewed above have modest content overlap PCS. The Hospital Anxiety and Depression Scale, for example, was developed specifically for the purpose of measuring emotional distress in medical patients. It includes mainly affective (e.g., sadness) and cognitive (e.g., worry) features of depression and anxiety. The Impact of Events Scale, also used in several studies, measures intrusive re-experiencing, avoidant coping, and hyperarousal features of post-traumatic stress. Of the individual symptoms that patients with MTBI endorse towards an ASD diagnosis, many have little overlap with classic PCS symptoms, such as hypervigilance (61%), fear (38%), distress on exposure (28%), derealization (25%), and startle response (19% [32]). Poor concentration and irritability had relatively low predictive power for ASD in an MTBI sample compared to other ASD symptoms [32].

Some authors have tried to minimize this confound by excluding items from psychological measures that have content overlap with PCS measures. For example, Lange et al. [50] created their depression group by including only the sadness, guilt, worthlessness, death ideation, and suicidal ideation diagnostic criteria. They still found an additive effect of MTBI and depression on PCS symptom reporting. Similarly, even after excluding irritability and difficulty concentrating from their PTSD measure, in-theatre PTSD was more associated with health outcomes following deployment than MTBI exposure in a military sample [71].

In summary, both the “third common-causal variable” (brain injury) and the artefact of syndromal overlap explanations appear to contribute to the psychological distress-PCS association, but not fully account for it. We conclude that the relationship between early psychological distress and PCS is, to a significant degree, a causal one, in which PCS symptoms cause psychological distress and vice versa.

3. Does psychological distress increase over time in patients who do not recover?

Based on the evidence available to him at the time, Lishman concluded that neurological factors diminish fairly rapidly after MTBI (i.e., weeks to months). Studies since then, using technologies such as electrophysiology (e.g., [29]), functional magnetic resonance imaging [42], magnetic resonance spectroscopy [7], and diffusion tensor imaging [80], have detected residual brain dysfunction in some patients. However, the neurobiological effects of MTBI, especially in the mildest forms of this injury, appear to be mostly time-limited, and the neurocognitive and neurobehavioral consequences of structural damage improve, at least partially, over time [38, 57]. A modern conceptualization of the neurobiology of MTBI is that the pathophysiology occurs on a spectrum from completely reversible to permanent structural and/or microstructural damage. All injuries exceeding a certain threshold of magnitude, at the very least, will be associated with reversible neurometabolic derangements of cellular systems. Thus, all of these injuries will be associated with neurobiological improvement.

Researchers have noted, however, that patients who remain highly symptomatic in the chronic phase, on average, reported similar symptom severity in the acute phase [43, 57, 81]. If PCS symptoms remain stable despite (at least partial) neurobiological recovery, a corollary of Lishman’s hypothesis must be that this neurobiological recovery is masked or offset by an increase in psychological distress. Few studies have documented the course of psychological distress vis-a-vis neurobiological recovery. However, there is some evidence that psychological distress does not increase over time in most patients.

The natural history of psychological distress has been described in overall MTBI samples (i.e., combined good and poor outcome groups). The few studies that prospectively tracked distress over the first week provide conflicting results about its acute course [25, 37]. Emotional symptoms are consistently found to be less common than certain other PCS symptoms around the first week (e.g., headache and dizziness) and decrease at a slower pace, such that somatic and cognitive symptoms catch-up by three months post injury [21,
4. Does the relationship between psychological distress and PCS symptoms increase over time?

Central to Lishman’s hypothesis is that the relationship between psychological distress and PCS grows stronger over the “many weeks to months” (p. 468) after MTBI. We identified two prospective studies that provided data to directly address this prediction. As noted above, Snell [81] reported large effect sizes for anxiety and depression between patients with versus without PCS at six weeks post injury. These effect sizes were very similar between the same groups six months later. That is, there was no trend for a strengthening relationship between psychological distress and PCS. However, Meares et al. [62] found that the relationship between severity of PTSD symptoms and PCS was 2.66 times stronger at three month follow-up compared to the initial assessment five days post injury. Unfortunately, these two studies provide seemingly contradictory evidence but also have major methodological differences (most notably, the timing of the assessments) that might explain the discrepancy.

Most of the literature on the relationship between psychological distress and PCS is cross-sectional and conducted with patients with remote MTBI. As previously mentioned, time since injury can be examined as a moderator variable. One recent meta-analysis examined longitudinal studies have administered psychological measures soon after MTBI and evaluated their ability to predict later outcome, and therefore allow us to address this question.

The King [44] study described earlier also collected outcome data at three months post injury. Univariate correlations between the psychological measures shortly after injury and PCS symptoms at follow-up were very similar to the correlations between these two measures in the acute phase. That is, the bivariate re-

5. Does early psychological distress predict later PCS?

If psychological factors are important for the maintenance but not initial development of the PCS, as Lishman proposed, they would have little prognostic value. In other words, if psychological functioning was weakly associated with PCS symptoms in the acute stage and only became strongly associated with the syndrome in the chronic stage, then psychological factors would be unable to predict which patients will go on to have a good or poor recovery. Fortunately, several prospective longitudinal studies have administered psychological measures soon after MTBI and evaluated their ability to predict later outcome, and therefore allow us to address this question.
lations between psychological distress and PCS symptoms were the same concurrently and prospectively. In a stepwise regression analysis with acute post-injury measures as predictors and PCS symptoms at follow-up as the dependent variable, King [44] found that only the anxiety subscale of the Hospital Anxiety and Depression Scale was a significant predictor, possibly due to multicollinearity between the psychological measures. Anxiety explained 30% of the variance in outcome. Notably, duration of post-traumatic amnesia and neuropsychological testing explained another 44% of the variance over and above anxiety, even though these measures had negligible univariate associations with PCS symptom severity.

King et al. [45] attempted to replicate these findings with a new sample. There were a few key differences in this cross-validation study: the sample was less severely injured (mean post-traumatic amnesia duration was 3.4 hours, SD = 4.7), the follow-up time point was six months, and most of the neuropsychological tests were dropped from the assessment battery. Acute post-injury anxiety was again a strong predictor of PCS symptoms at follow-up, explaining 20% of the variance. Acute PCS symptoms and duration of post-traumatic amnesia did not explain any additional variance.

Stulemeijer et al. [86] conducted comprehensive assessments on average nine days (range = 0 to 37) after MTBI (notably, 40% of their sample had a trauma-related intracranial abnormality on CT). They defined two favorable outcomes at six months post injury, low PCS symptoms (“mild” or “no” ratings for at least 13/16 symptoms) and full return to work. In their univariate analysis with low PCS symptoms as the outcome, high education (OR = 5.4), absence of comorbid physical injury (OR = 5.5), initial low PCS symptom severity (OR = 6.3), and low levels of post-traumatic stress on Impact of Events Scale (OR = 16.1) were significant. Multivariate analyses with backwards stepwise regression revealed that post-traumatic stress had the strongest predictive power (odds = 10.0) of any variable. In the analyses with return to work as the outcome, post-traumatic stress was non-significant, whereas low education, peri-injury nausea or vomiting, additional extracranial injury, and early post-injury severe pain were associated with decreased likelihood of returning to work.

Snell [81] reported six-month outcome data from the sample described in Snell et al. [82]. Acute post-injury psychological functioning was associated with outcome at follow-up. Specifically, the anxiety and depression subscales of the Hospital Anxiety and Depression Scale had Cohen’s d effect sizes of 0.5 and 0.6, respectively. The anxiety subscale also made a unique contribution to the prediction of PCS symptom and disability severity at follow-up.

Meares et al. [62] reported the results from following their original samples of MTBI patients and trauma controls [61] over three months. In a multivariate analysis with acute post-injury predictors and PCS status at follow-up as the dependent variable, Acute Stress Disorder scores (OR = 1.05) and pre-injury history of psychiatric diagnosis (OR = 2.99) emerged as significant. Pain and neuropsychological performance were not associated with PCS at follow-up. Injury type (MTBI vs. non-head injury) did not predict PCS, and in participants with MTBI, duration of post-traumatic amnesia also did not predict PCS.

It has been well-documented that early PCS symptom severity predicts PCS status at follow-up [43,92]. Dischinger et al. [21] examined the prognostic value of different early PCS symptom clusters. Endorsing emotional symptoms (anxiety, depression, and/or irritability) within 3 to 10 days post-MTBI was the strongest predictor of three-month PCS status, and was associated with an 8.4-fold risk. Anxiety was the strongest single symptom predictor, but interestingly, only in women.

In summary, early psychological distress predicts MTBI outcome. Importantly, this has been replicated in multiple studies, some of which include distress in multivariate models where neuropsychological performance and measures of injury type and severity have relatively little predictive power. Similar findings have been reported for whiplash injury after a motor vehicle accident [47]. These data support the view that early psychological functioning at least partly causes the trajectories of good and poor outcome to begin to diverge.

6. The etiology of the post-concussion syndrome revisited

We identified four predictions that follow from Lishman’s hypothesis and evaluated the evidence for/against them that has emerged over the last 20 years. Unfortunately, the available evidence is still insufficient for a definitive answer, but allows us to tentatively conclude that psychological factors play a prominent etiological role from the earliest stages of recovery from MTBI. This is based on evidence that psychological distress (a) is fairly common in the initial days after an
MTBI and correlates with initial PCS severity, an association that cannot be fully explained by a third common variable (brain injury) or as an artefact of syndromal overlap with comorbid psychiatric disorders; (b) appears to remain fairly stable in patients who fail to recover (in group studies); (c) may not become more prominent over the course of PCS (this remains poorly understood); and (d) is among the best acute stage predictors of late PCS outcome. A summary of our review of the four predictions is presented in Table 1.

Lishman noted that most investigations of the psychology of PCS are carried out with the minority of patients who have persistent disabling symptoms. This holds true today. Studies of this type do little to advance our knowledge of whether and how psychological factors influence PCS differently (in quantity or quality) from the acute to chronic phase. Prospective research that tracks the course of psychological distress and its relationship to PCS over time is most needed.

At present, a biopsychosocial conceptualization of the development and maintenance of the post-concussion syndrome best fits the data. That is, both biological and psychosocial factors can contribute to PCS throughout its course — and there are likely considerable individual differences in their relative contributions [75]. A theoretical biopsychosocial model is presented in Fig. 1. Definitions of selected terms are presented in Table 2. A detailed discussion of this biopsychosocial model is beyond the scope of this article, but the interested reader can refer to a number of sources for additional information [40,41].

It is important to appreciate that each person enters an injury event with a diverse range of individualized genetic, developmental, social, psychological, and biological resilience and vulnerability factors that contribute to both good and poor outcome [39,93]. Many of these vulnerability factors have been studied in biological psychiatry, clinical psychology, and health psychology, but most have not been well studied in the context of MTBI. To advance our understanding of both good and poor outcome, it will be important to design studies that more fully examine pre-injury characteristics.

Characteristics of the injury event that influence outcome include the biomechanics of the head trauma; injury to the neck or other parts of the body; contextual circumstances (e.g., accident vs. assault); and the person’s acute psychological reaction. In the acute phase following injury (e.g., the first two weeks), a diverse set of factors can cause and amplify physical, emotional, and cognitive symptoms. An injury to the brain is not the only cause of initial symptoms. Vestibular injury, neck and bodily injury, psychological distress, and maladaptive coping behaviors can cause the same symptoms seen in PCS, and they can exacerbate PCS symptoms.

When conceptualizing PCS post-acutely (e.g., 1–3 months) or chronically (12 months), it is well established in the literature that these symptoms are non-specific; they can arise from other conditions, singly or in combination, such as chronic headaches, chronic bodily pain, depression, or PTSD. These symptoms are also common in the general population and in people with medical problems. The nature and extent of symptoms reported by individual patients can be influenced by psychological distress, social psychological factors (e.g., good-old-day bias, the nocebo effect, iatrogenesis, and misattributions), and personality characteristics (e.g., pre-injury personality traits). A biopsychosocial conceptualization, with an emphasis on comprehensive assessment and differential diagnosis, has important implications for treatment.

7. Implications for early intervention, treatment and rehabilitation

Given that there is now clear evidence that early psychological distress is relevant in the development and
course of PCS, early intervention targeting psychological distress might help reduce symptom burden and prevent the development of a chronic condition. Education and reassurance has become the standard practice for routine intervention at concussion clinics and in primary care. When delivered early, this intervention for routine intervention at concussion clinics and prevention methods are lacking. Individualized coaching for symptom management and activity resumption has been shown to improve outcomes in consecutively recruited MTBI samples [8,64]. These more extensive early interventions may be preferable to education/reassurance for individuals with acute distress, but finding that reassurance is notoriously unhelpful in patients with high healthy anxiety, and also partly responsible for maintaining high levels of anxiety [14,77].

Reassurance alone probably cannot overcome strongly held maladaptive beliefs after MTBI. Screening for psychological distress and maladaptive beliefs after MTBI could help identify individuals who require more than usual care, and could benefit from psychological intervention. However, further research is needed to inform how screening should be done and what kind of intervention. For patients who meet criteria for Acute Stress Disorder after MTBI, early trauma focused cognitive-behavioral therapy should be considered [16]. However, for the higher proportion who present with subclinical psychological distress, evidence-based PCS prevention methods are lacking. Individualized coaching for symptom management and activity resumption has been shown to improve outcomes in consecutively recruited MTBI samples [8,64].

Fig. 1. A biopsychosocial conceptualization of poor outcome from mTBI. For example, hypertension, heart disease, cardiac surgery, diabetes, thyroid problems, and small vessel ischemic disease. Note: Structural and/or microstructural damage to the brain is not necessary to cause or to maintain the symptoms comprising a post-concussion syndrome. Moreover, structural and/or microstructural damage, if present, is likely insufficient to causally maintain a persistent post-concussion syndrome. Assuming that a constellation of persistent symptoms are present (i.e., not exaggerated), there are many factors that could, singly or in combination, be the underlying cause of these symptoms. Notably, patients with chronic pain frequently report a constellation of symptoms that are post-concussion-like, and patients with depression are virtually guaranteed to report symptoms that mimic a post-concussion syndrome (in the absence of a history of head trauma). Copyright © 2011, Grant L. Iverson. Used with permission.
Vulnerability: Conceptualized as a superordinate composition of individual risk factors for physical and mental health problems.

Challenge refers to a belief system in which wisdom and growth are gained from difficult experiences. A person turns events into something meaningful and important. Control refers to the belief that one can influence the course of events. Hardiness refers to a belief system in which wisdom and growth are gained from difficult experiences.

Hardiness: A personality characteristic consisting of three psychological attitudes and beliefs: commitment, challenge, and control. Through commitment, a person turns events into something meaningful and important. Control refers to the belief that one can influence the course of events. Challenge refers to a belief system in which wisdom and growth are gained from difficult experiences.

Cognitive Hypochondriasis and Preoccupation: Hypochondriasis and Somatic Preoccupation have been recognized as dysfunctional behavior patterns for decades. They are associated with a magnified perception of bodily sensations and symptoms, fear of having serious health problems or disease, and extensive contact with health care providers. By extension, Boone [11] discussed a form of cognitive hypochondriasis that sometimes occurs in patients with poor outcome following MTBI. These patients have a fixed belief that they are significantly cognitively impaired, despite normal neuropsychological test performance, and that this impairment reflects permanent brain damage. Delis and Wetter [19] proposed a “Cogniform Disorder,” a Somatoform Disorder Subtype, characterized by pervasive and excessive cognitive symptoms and conversion-like style changes over time, through environmental factors and social reinforcement, to include verbal and nonverbal illness behaviors.

Neuroticism: A personality trait characterized by a strong tendency to experience negative emotions such as anxiety, depression, anger, and self-consciousness. Individuals with this trait have considerable difficulty coping with stress.

Reinforced Illness Behavior: Some patients with chronic pain conditions and somatoform disorders develop entrenched reinforced illness behaviors and evolve into describing their symptoms and problems in a dramatic or exaggerated manner. That is, their behavior and interpersonal style changes over time, through environmental factors and social reinforcement, to include verbal and nonverbal illness behaviors.

Nocebo Effect: The nocebo effect is the causation of sickness by the expectations of sickness and by associated emotional states. That is, the sickness is, essentially, caused by expectation of sickness [31].

Perceived Injustice: A strongly held belief that one has been treated unfairly, disrespectfully, and/or thwarted in what one feels entitled to. Believing that one is suffering unnecessarily as a result of another’s actions can underlie perceived injustice. This can be a firmly entrenched belief system that can influence the perception and reporting of symptoms, treatment adherence, and health-related behaviors.

Perfectionism: A personality characteristic characterized by an organized, disciplined, and focused striving toward perfection in behavior and activities. It can be particularly pathological when a person with high levels of neuroticism believes firmly that anything less than perfection is unacceptable.

Resilience: This is comprised of a diverse set of biological, psychological, and social factors that confer some degree of protection from physical and mental health problems. From a psychological perspective, resilience is an intrinsic characteristic underlying a person’s ability to successfully adapt to acute stress and more chronic forms of adversity.

Type D Personality: This personality pattern is characterized by two stable personality traits: negative affectivity and social inhibition.

Unconscientiousness: A personality trait characterized by reduced self-discipline and ambition, disorganization, and a more lackadaisical approach to life.

Vulnerability: Conceptualized as a superordinate composition of individual risk factors for physical and mental health problems.
their efficacy in this at-risk subgroup has not yet been studied. A better understanding of the specific psychological factors that contribute to the development of PCS (e.g., maladaptive illness beliefs) will inform future PCS prevention research efforts [83].

Some patients will have chronic symptoms. Comorbid conditions, such as depression, generalized anxiety disorder, PTSD, chronic pain, insomnia, and chronic vestibular problems can be the primary cause of these longstanding symptoms. As a guiding principle: Treat what you can treat. Recommendations for treatment and rehabilitation flow from comprehensive assessment. If a person is deconditioned, anxious, depressed, drinking too much alcohol, and sleeping poorly, it is very likely that he or she would feel cognitively impaired, and have trouble functioning at work and in daily life, due to a diverse range of symptoms (e.g., headaches, fatigue, and emotional instability). As such, treatment can be focused on specific symptom target areas, such as improving sleep hygiene and reducing alcohol use.

Psychological treatments are effective for reducing symptoms and improving functioning in patients with depression [12,23] and depression with comorbid medical problems [9,89]. Combining medications and psychotherapy tends to yield the best outcome [68]. If adequately treated, then some people with depression can experience a substantial improvement in their cognitive functioning [27,34,51]. Psychological treatment is also effective for generalized anxiety disorder [36], social anxiety disorder [1], and PTSD [10], and there is some evidence that psychological treatment can reduce symptoms in patients with comorbid mild TBI and anxiety problems [84]. Psychological and behavioral treatments can also be effective for improving sleep and reducing psychological distress in people with insomnia [96]. It is important to aggressively treat chronic pain, and it is often helpful to focus treatment and rehabilitation services on co-occurring chronic pain and anxiety [6]. Chronic vestibular problems, with associated tinnitus, dizziness, nausea, and balance difficulty, magnify psychological distress in many people. Vestibular rehabilitation can be effective for some people [4].

In general, the primary goal of treatment and rehabilitation for those who have persistent symptoms and comorbidities is to reduce symptom burden and improve functioning. The goal is to provide timely, high quality, evidence-based treatment and rehabilitation services that target the specific needs of the individual. In complex cases, such as for patients who experienced multiple bodily injuries in addition to an MTBI, specialized, interdisciplinary assessments are often necessary to define the problem areas and to generate a treatment plan. Treatment and rehabilitation services can be provided simultaneously and sequentially. It is important to appreciate that improvement in one area (e.g., insomnia, chronic pain, or anxiety) often leads to concomitant improvement in other areas (e.g., depression and cognitive functioning).

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