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Anxiety symptoms and disorders in the first year after sustaining
mild traumatic brain injury

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Impact and Implications Statement

- Anxiety symptoms and disorders are frequent in the first year after mTBI compared to one-year prevalence rates the general population.
- Anxiety seems to exacerbate or prolong mTBI-related symptoms including fatigue, irritability, perceived stress, depressive symptoms, pain, sleep difficulties and cognitive difficulties.
- Clinicians should consider monitoring anxiety symptoms more systematically early-on after a mTBI in order to provide preventive or therapeutic interventions.

Abstract

Purpose/Objective: The goals of the present study were (1) to document the prevalence of anxiety-related disorders and anxiety symptoms at 4, 8, and 12 months post-injury in individuals with mild traumatic brain injury (mTBI) while considering pre-injury history of anxiety disorders and (2) to verify whether the presence of anxiety in the first months following mTBI was associated with more symptoms present one year after the injury. **Research Method/Design:** One hundred and twenty participants hospitalized after an accident and having sustained mTBI were assessed at 4, 8, and 12 months post-accident with the Mini-International Neuropsychiatric Interview, the Hospital Anxiety and Depression Scale and questionnaires assessing fatigue, irritability, perceived stress, cognitive difficulties, depression, insomnia, and pain. **Results:** At 4 months, 23.8% of participants presented with at least one anxiety-related disorder compared to 15.2% at 8 months and 11.2% at 12 months. Overall, 32.5% presented with at least one anxiety disorder over the first 12 months post-mTBI. Participants with a history of anxiety (20.5%) were significantly more anxious following their accident. Individuals who were anxious 4 months after the accident presented with more symptoms in different areas 12 months post-injury compared to non-anxious individuals. **Conclusions/Implications:** The present results highlight that anxiety should be evaluated and managed carefully as it appears to be a key factor in the persistence of other mTBI-related symptoms.

Keywords: Anxiety; mild traumatic brain injury (mTBI); long-term outcomes; persistent symptoms

Introduction

Mild traumatic brain injuries (mTBI) represent 80 to 90% of all traumatic brain injury (TBI) cases treated either in a hospital or an emergency department (Skandsen et al., 2019). Following mTBI, individuals often present with somatic, psychological and cognitive symptoms of varying duration. The most common are fatigue, headaches, confusion, dizziness, blurred vision, sleep disturbances, difficulty with memory and concentration, depression, anxiety and irritability (Bergersen, Halvorsen, Tryti, Taylor, & Olsen, 2017). In the weeks following mTBI, between 38 and 80% of individuals will present symptoms, but the majority will make a full recovery and no longer be symptomatic after 3 to 12 months (Nelson et al., 2019). However, it is estimated that up to 48% of people having suffered a mTBI may have symptoms which persist three months or more after the accident (Ruff & Jamora, 2009; Theadom et al., 2016). It remains a challenge to predict who will experience prolonged symptoms following mTBI because a wide variety of medical, psychological, social, and contextual risk factors influence recovery (Marshall et al., 2018).

Symptoms of depression and anxiety are frequent following mTBI, and may even persist up to several years post-injury (Barker-Collo et al., 2018). These psychological symptoms possibly have a role to play in crystalizing other mTBI-related symptoms. For example, several authors have suggested that depression and anxiety symptoms measured in the days following mTBI are potential predictors of mTBI symptoms persisting a minimum of three months after the accident (Clarke, Genat, & Anderson, 2012; Dischinger, Ryb, Kufera, & Auman, 2009; Meares et al., 2011; Snell, Hay-Smith, Surgenor, & Siegert, 2013). There is still very little research specifically addressing anxiety following mTBI (Moore, Terryberry-Spohr, & Hope, 2006). Anxiety may encompass a variety of manifestations (e.g. worrying, agitation, restlessness, tension, fear) of varying severity, up to full-blown disorders, including generalized anxiety

disorder, social phobia, and panic disorder (with and without agoraphobia). Adjustment disorder can also present with anxious features. Up until the publication of the DSM-5, post-traumatic stress disorder (PTSD) and obsessive-compulsive disorder were considered anxiety disorders. PTSD has been studied extensively after mTBI, even though it is not necessarily the most common anxiety-related disorder (Moore et al., 2006). Other anxiety-related disorders have not been well documented in this population. Meares et al. (2011)'s reported rates of several anxiety disorders three months post-mTBI in comparison to an orthopedic trauma control group. They used the Mini-International Neuropsychiatric Inventory (MINI), a semi-structured interview based on the Diagnostic and Statistical Manual of Mental Disorders (DSM), and found that 32.1% of individuals having suffered a mTBI presented with at least one anxiety disorder diagnosis in the first three months post-injury. For the mTBI group and the orthopedic control group respectively, they found rates of 7.1% and 0% for obsessive-compulsive disorder, 10.7% and 3.4% for panic disorder with or without agoraphobia, 10.7% and 12.1% for generalized anxiety disorder and 3.6% and 5.2% for social phobia. According to other studies which used validated questionnaires measuring symptoms of anxiety, between 22% and 24% of participants present with clinically significant symptoms of anxiety 6-12 months post-mTBI (Mooney & Speed, 2001; Spitz, Schönberger, & Ponsford, 2013).

The etiology of anxiety presenting after a mTBI remains unclear. Some authors have suggested that pre-frontal cortex dysfunction may be linked to the appearance of anxiety (Rauch, Shin, & Phelps, 2006). Other authors have hypothesized that the injury causes a temporary psychological vulnerability to the development of psychological disorders, particularly given the multiple stressors experienced during the accident per se, transfer to a hospital, hospitalisation or adaptation to mTBI-related deficits (Mooney & Speed, 2001). Increasing mediatisation and public awareness about mTBI and sports-related concussions, bringing about its share of mixed

messages, may also feed into the anxiety of some individuals about having another injury (e.g. fear of second impact syndrome), about having long-term injury-related symptoms (e.g. fear of having enduring cognitive issues) or about having serious brain dysfunction caused by the mTBI in later life (e.g. fear of developing dementia) (King, 2019). A history of mental health issues may also increase the rate of vulnerability to post-TBI anxiety disorders (Moore et al., 2006). Indeed individuals with a history of psychological disorders are more vulnerable to developing anxiety and have fewer adaptive strategies (Ponsford et al., 2012). According to Gould, Ponsford, Johnston, and Schönberger (2011), individuals who previously suffered from an anxiety disorder are nine times more likely to suffer from an anxiety disorder after their injury compared to those who have never had an anxiety disorder (Gould et al., 2011). Regardless of the source of anxiety, a precise picture of the nature and prevalence of anxiety disorders and the severity of anxiety symptoms would be useful to guide interventions in this population.

The role anxiety might play in the recovery process following mTBI also remains unclear. Anxiety may influence how individuals experience TBI-related symptoms, possibly by exacerbating or contributing to prolong certain symptoms (Dischinger et al., 2009), such as heightened vigilance to symptoms or catastrophizing. Regarding injury severity, it has been suggested that persons with mild injuries can be particularly aware of their deficits and of subtle changes in their functioning, much more so than persons who have sustained moderate or severe TBI and who might have some level of anosognosia or decreased awareness of their deficits (Gould et al., 2011; Lux, 2007; Wallace & Bogner, 2000).

In sum, few studies have focused specifically on post-TBI anxiety and on its evolution following the injury, even fewer on understanding how anxiety can influence the trajectory of recuperation in the long-term after a mTBI. Given these knowledge gaps, the first objective of this study was to document the prevalence of anxiety disorders and anxiety symptoms at 4, 8, and

12 months post-accident in individuals having been hospitalized after an accident where they suffered mTBI while taking into consideration pre-injury history of anxiety disorders. We expected the global prevalence of anxiety-related disorders over the first year to be higher than in the general population, and hypothesized that persons with a history of anxiety disorders would present more anxiety-related disorders and higher severity of anxiety symptoms post-injury. The second objective aimed to verify if the presence of anxiety measured in the first few months following mTBI (i.e. up to 4 months) was associated with longer-term (i.e. 12 months post-injury) presence of clinically significant symptoms in various spheres, namely fatigue, irritability, perceived stress, cognitive difficulties, depression, insomnia and pain. We hypothesized that compared to participants without significant anxiety, the sub-group presenting with anxiety at 4 months would present significantly more symptoms at 12 months post-injury.

Methodology

Participants

This is a secondary analysis of a larger study on post-TBI mental health including persons who were admitted to the hospital after an accident and who were diagnosed with mild to severe TBI (Ouellet et al., 2018). One hundred and twenty individuals aged 18 to 65 years who were hospitalised at the *Hôpital de l'Enfant-Jésus du Centre hospitalier universitaire de Québec* after a mTBI participated were included in the present study. The cause of hospitalization was not necessarily mTBI, as some patients may have been admitted to the hospital because of other injuries or conditions. Persons having incurred mTBI who visited the Emergency Department (ED) but who were not hospitalised were not included in the study. Exclusion criteria were: (1) a history of neurological disorder preceding the TBI (i.e. moderate or severe TBI, stroke, brain

tumor); (2) concomitant spinal cord injury; (3) inability to understand written or oral information or to provide informed consent (due to severe cognitive or language comprehension deficits).

Measures

Presence of anxiety or anxiety-related disorders

Anxiety or anxiety-related disorders were assessed at 4, 8, and 12 months post-mTBI using the French version of the Mini-International Neuropsychiatric Interview (Sheehan, 2014). This is a semi-structured interview which allows for the assessment of multiple Axis 1 mental disorders according to the DSM-IV-TR (the study was initiated before the publication of the DSM-5). During the first interview, lifetime history of mental disorders (up to the time of injury) was also documented. This diagnostic interview is validated in French and English and has been previously used with a mTBI population (Meares et al., 2011; Ponsford et al., 2012). The diagnoses of interest assessed for this study were: generalized anxiety disorder, post-traumatic stress disorder, social phobia, panic disorder (with and without agoraphobia), obsessive-compulsive disorder, adjustment disorder with anxiety or with mixed anxiety and depressed mood, and mixed anxiety-depression disorder. The use of this last diagnostic category (part of the research criteria sets “for further study” in the DSM-IV-TR) was motivated by the fact that clinicians working with individuals having suffered TBI often report that their clients present simultaneously with symptoms of depression and anxiety which cause significant distress. Furthermore, this condition seems to be quite frequent in primary care, and some clinicians have argued that it should be included in the DSM to increase access to treatment (Möller et al., 2016). A conservative approach was used when attributing a diagnosis on the basis of the MINI; a diagnosis was only given if all criteria were met and if there was clearly significant distress. It should also be noted that no diagnosis of generalized anxiety disorder was attributed at 4 months

if it was not present before the accident, because the DSM-IV-TR clearly states that the symptoms must be present for more than six months in order to pose a diagnosis.

Anxiety symptoms

The severity of anxiety symptoms was assessed at 4, 8, and 12 months post-mTBI with the anxiety subscale of the Hospital Anxiety and Depression Scale (HADS-A) (Zigmond & Snaith, 1983). The global HADS instrument includes two subscales, one for anxiety and one for depression, and excludes somatic symptoms, for example sleep difficulties or changes in appetite, which can be caused by certain medical conditions. Schönberger and Ponsford (2010) examined the reliability and factor structure of the HADS in a TBI population. They were able to reproduce the original three-factor structure of the instrument and found that both subscales had high reliability (Schönberger & Ponsford, 2010). A French version of the HADS has also been validated (Savard, Laberge, Gauthier, Ivers, & Bergeron, 1998). The anxiety subscale of the HADS is composed of 7 items assessing the presence of anxiety symptoms over the past week scored on a four-point Likert scale (0 to 3). A global score of 8 or more is considered clinically significant (Olsson, Mykletun, & Dahl, 2005). In the present study, a continuous score on the HADS-A subscale was used as a measure of severity of anxiety symptoms, whereas a dichotomous score (below or above the cutoff score of 8) was used as an indicator of presence of clinically significant anxiety symptoms.

Fatigue

The Multidimensional Fatigue Inventory is composed of 20 items scored on a five-point Likert scale (Smets, Garssen, Bonke, & De Haes, 1995). The questionnaire measures five dimensions of fatigue experienced in the past few days: general fatigue, mental fatigue, physical fatigue, decrease in activities and decrease in motivation. Total scores vary from 4 and 20 for each subscale. The higher the score, the greater the fatigue. Internal consistency and construct validity

are adequate and the psychometric properties of a French-Canadian version have been shown to be equivalent to the original tool (Fillion, G  linas, Simard, Savard, & Gagnon, 2003).

Anger and irritability

The anger/irritability subscale of the *Indice de d  tresse psychologique de l'Enqu  te Sant   Qu  bec* comes from the French translation of the validated Psychiatric Symptom Index (Ilfeld, 1976). It contains four questions regarding anger, irritation and negativity. Participants were asked to answer these items using a four-point Likert scale (never to very often) and higher total scores indicate greater irritability.

Perceived Stress

A French-Canadian version (Morin, Rodrigue, & Ivers, 2003) of the Perceived Stress Scale was used. This is a 14-question tool using a five-point Likert scale (never to very often) (Cohen, Kamarck, & Mermelstein, 1983). Participants evaluate the frequency of thoughts or feelings related to stressful situations over the past month. Higher scores are indicative of higher levels of perceived stress, unpredictability and a lack of control over one's life. The tool presents high reliability and is correlated with stressful life events, depression and anxiety symptoms (Cohen, Kamarck, & Mermelstein, 1983).

Cognition

To measure complaints relative to cognitive functioning, MacKenzie et al. (2002) proposed the addition of a cognitive subscale (COG) to the Medical Outcome-Short Form Health Survey (SF-36) for studies focusing on various traumas. This subscale is comprised of four items evaluating difficulties with reasoning and problem-solving, memory of recent events, sustaining attention and concentration. A French version of this tool has previously been used with a TBI sample but the psychometric properties of the instrument have not been formally evaluated (Ouellet, Sirois, & Lavoie, 2009).

Depressive symptoms

The severity of depressive symptoms at 4, 8 and 12 months post-mTBI was measured with the depression subscale of the Hospital Anxiety and Depression Scale (Zigmond & Snaith, 1983, see above for more information). This 7-item subscale (HADS-D) assesses depressive symptoms over the past week. Subscale scores of 8 or more corresponding to clinically significant symptoms.

Sleeping difficulties

The French version (Blais, Gendron, Mimeault, & Morin, 1993) of the Insomnia Severity Index was used (Morin, 1993). This is a 7-item tool using a 5-point Likert scale where the participant evaluates his/her : (1) severity of difficulties with falling asleep, staying asleep and early morning awakenings, (2) current satisfaction with sleep, (3) interference of sleep difficulties with daily functioning, (4) noticeability of impairment due to sleep difficulties and (5) level of distress caused by the sleep issues. The participant answered each item while considering the past month. Total scores vary between 0 and 28 (0-7: no clinically significant insomnia, 8-14: sub-clinical insomnia, 15-21: moderate insomnia, 22-28: severe insomnia). This tool has adequate internal consistency, concurrent validity and sensitivity (Bastien, Vallières, & Morin, 2001).

Pain

The two items of the pain subscale of the SF-36 were used to assess the intensity (none to severe) and interference (none to a lot) of pain in daily activities (Ware, Snow, Kosinski, & Gandek, 2000). The SF-36 is a psychometrically sound tool with well-defined norms frequently used in epidemiological studies. It has been used previously in persons with TBI (Findler, Cantor, Haddad, Gordon, & Ashman, 2001). For the purpose of the present study only the scores from both pain-related questions were used and combined into a global score ranging from 0-100.

Procedure

The study was approved by the Ethics Review Board of the Level I trauma center of the *Hôpital de l'Enfant-Jésus du Centre hospitalier universitaire de Québec*. A research nurse first consecutively identified all potential patients, and met them at their bedside or before hospital discharge. She gave them an information brochure about the study and obtained verbal consent to contact them at a later time. About three months post-injury, a research coordinator contacted participants to provide them with additional information about the study. If they agreed to participate, a consent form was sent out by mail and sociodemographic information was collected. Interviews and questionnaires were administered at 4, 8, and 12 months after the injury. The interviews took place in person at the *Institut de réadaptation en déficience physique de Québec, Canada* or by phone. Questionnaires were mailed or given directly to the participants before each interview. Interviews were administered by qualified and trained interviewers (3 licensed psychologists, five psychology doctoral students). The team of interviewers met approximately once a month to review complex cases, discuss issues with differential diagnosis and to reach consensus. Participants received a 20\$ monetary compensation for each completed assessment. Table 1 presents the socio-demographic and clinical characteristics of the sample.

Insert Table 1 here

Statistical analyses

In order to determine if anxiety rates differed from one measurement time point to another and according to pre-injury history of anxiety (Objective 1), generalized linear models were applied (GEE). Three dependant variables were selected: (1) the proportion of individuals presenting with a diagnosis on the MINI, (2) the proportion of persons above or below the cut-off scores (≥ 8 or <8) on the HADS-A and (3) the average score on the HADS-A. Thus, three 2 X 3

GEEs were computed: History of anxiety disorder (two-level non-repeated factor: presence or absence of pre-existing anxiety) \times Time (three-level repeated factor: 4, 8, and 12 months). These analyses are robust to missing data and allow specification of the correlation matrix related to longitudinal data. Non-structured autoregressive matrices and matrices of 1st order were tested. The former were selected given that the dependant variables did not meet the AR (1) matrix premises and because the corrected independence model (QICC) criteria were similar. For the continuous variable (HADS-A), a gamma distribution (log link) was specified, because the variable was not normally distributed. A binary logistic distribution was chosen for the two dichotomous variables. A Bonferroni correction (Dunn, 1961) was applied for multiple comparisons to control for α -error inflation. This method consists of comparing each p value to a specific α significance threshold, based on the following formula: $.05 \div$ number of comparisons. For time effects, three post-hoc comparisons were explored: 4 months versus 8 months, 4 months versus 12 months and 8 months versus 12 months. This corresponds to a critical value of .0167. For significant interaction effects, nine comparisons were carried out between both levels of the presence or absence of anxiety at all three time points, which corresponds to a critical value of .0056.

For objective 2, preliminary analyses were carried out with Student's *t*-tests to document the severity of symptoms at 12 months post-accident according to the presence or absence of anxiety at 4 months following mTBI. Then, a generalized linear model (GLM) analysis was carried out. A single non-repeated factor was used: the presence/absence of a clinically significant level of anxiety at 4 months, defined as the presence of a diagnosis of an anxiety disorder on the MINI *or* a score of 8 or higher on the HADS-A. The dependant variable was the *number of symptoms* recorded at a significant level at 12 months among the seven following symptoms: fatigue, irritability, perceived stress, cognitive difficulties, depression, insomnia and

pain. To calculate this variable for each participant, continuous scores of each symptom questionnaire were transformed into dichotomous scores in which a significant symptom corresponded to a score that was one standard deviation above the global sample's average (or one standard deviation below the average for cognitive difficulties and pain scales). Number of symptoms above threshold were then added up (count data). Since the data for this variable was not normally distributed, a negative binomial distribution with identity link was used in the analysis.

Results

Of all the individuals who met the inclusion and exclusion criteria for the larger data collection, 24.3% refused to participate, 10.3% were missed (could not be solicited by the research nurse) and 10.1% could not be reached even if they had agreed to participate. The global participation rate was therefore 55.3% of the targeted population. The sample was predominantly composed of men ($n = 91$, 75,8%) and most of them had completed a high-school education or less. The most frequent causes of mTBI were motorized vehicle accidents (44.2%) and falls (39.2%) (see Table 1). According to the medical files, 56% of the sample had complicated mild TBI because of evidence of a positive finding during neuroradiological exam (generally a CAT scan). The remaining participants had uncomplicated mild TBI.

Prevalence of anxiety disorders

Table 2 shows the rates of anxiety disorders according to the MINI and of clinically significant anxiety according to the HADS-A at pre-accident as well as 4, 8, and 12 months post-accident. The most frequent anxiety-related disorders were mixed anxiety-depression disorder, generalized anxiety disorder and post-traumatic stress disorder. Furthermore, according to the

MINI, 20.5% of participants presented with at least one anxiety-related disorder in their lifetime before the accident (see Table 2 for types of disorders). Post-injury, 23.8% presented with a disorder at the 4-month assessment, 15.2% at 8 months, and 11.2% at 12 months. Overall, 32.5% presented with at least one anxiety disorder over the first 12 months after their mTBI.

Insert Table 2 here

Anxiety over the first year according to pre-accident history of anxiety disorder

The results of the GEEs are presented in Table 3. For the presence/absence of anxiety disorders according to the MINI as the dependant variable (Quasi-likelihood corrected with a criteria of independence model [QICC] = 237.006), both the effects of time ($p = 0.011$), and pre-injury history of an anxiety disorder ($p = 0.000105$) were found to be significant. The interaction was not significant ($p = 0.154$). Individuals having a history of at least one pre-accident anxiety disorder were significantly more likely to present with anxiety disorders after the accident (Mean difference = - 0.31, SE = 0.094, CI [-0.49, -0.13]). After applying a Bonferroni correction, for the Time effect, only the comparison between the proportions of anxiety disorders at 4 and 12 months remained significant ($p = 0.002$), indicating that the proportion of anxiety disorders was significantly larger at 4 months than at 12 months (Mean difference = 0.18, SE = 0.06, CI [0.06, 0.30]). However, the History X Time interaction ($p = 0.154$) was not significant.

When examining the presence/absence of clinically significant anxiety symptoms on the HADS-A (QICC = 276.132), the effect of history of pre-injury anxiety disorder was significant ($p < 0.001$, Mean difference = - 0.47, SE = 0.10, CI [-0.67, -0.28]), but neither the effect of Time ($p = 0.540$) nor the History X Time interaction ($p = 0.393$) were significant.

For the continuous score on the HADS-A as the dependant variable (QICC = 121.837), the effect of pre-injury history was significant ($p < 0.001$, Mean difference = - 4.97, SE = 0.94, CI [-6.80, -3.13]), as was the History X Time interaction effect ($p = 0.042$). Following Bonferroni correction, results indicated that persons with a history of anxiety disorders had a higher average score on the HADS-A at 4, 8, and 12 months, compared to individuals without a pre-accident history of anxiety disorders ($p < 0.001$ for all 3 comparisons, Mean difference at 4 months = - 3.73, SE = 1.07, CI [-6.61, -0.85]; Mean difference at 8 months = - 5.47, SE = 1.14, CI [-8.75, -2.19]; Mean difference at 12 months = - 5.70, SE = 1.08, CI [-8.88, -2.52]). However, the effect of Time effect was not significant ($p = 0.770$).

Insert Table 3 here

Comparison of anxious and non-anxious individuals at 4 months post-mTBI on symptoms at 12 months post-mTBI

The Student's *t*-test results (Table 4) indicate that, compared to non-anxious individuals, persons who were anxious at 4 months post-injury had significantly higher averages on the fatigue, irritability, perceived stress, depressive symptoms, pain, sleep difficulties and cognitive difficulties scales 12 months after the accident. Complete data was available for 78 patients for the generalized linear model (Corrected Akaike Information Criterion [AICC] = 216.194). This analysis revealed significant differences between groups (Wald χ^2 (1, N = 78) = 9.937, $p = 0.00162$; B= -1.55, SE= 0.49, CI [-2.52, -0.59]), indicating that individuals who were anxious 4 months after the accident presented with a greater number of symptoms 12 months post-accident than individuals who were not anxious at 4 months following TBI. Anxious individuals at 4

months post-injury displayed an average of 4.38 clinically significant symptoms at 12 months compared to 1.16 symptoms in non-anxious individuals.

Insert Table 4 here

Discussion

This study aimed at documenting the prevalence of anxiety-related disorders and symptoms of anxiety at 4, 8, and 12 months post-injury in individuals having suffered a mTBI while also considering their pre-injury history of anxiety disorders. Overall, 32.5% fulfilled the DSM-IV criteria for an anxiety-related disorder during the first year after mTBI. Participants who had a history of anxiety disorders preceding the injury were significantly more likely to present with anxiety disorders and symptoms after the accident. Fortunately, there was a significant reduction in the frequency of anxiety disorders between 4 and 12 months post-mTBI. Considering that almost a third of the sample suffered from an anxiety disorder in the first year post-injury, this rate is 2.5 times higher than the one-year prevalence rate of anxiety disorders in the general Canadian population, which is 11.6% (O'Donnell, Cheung, Bennett, & Lagacé, 2016). Longitudinal findings also showed that participants who were significantly anxious at 4 months post-mTBI presented with a higher number of symptoms at 12 months post-mTBI compared to those who were not. This suggests anxiety could play a role in the persistence of other mTBI-related symptoms.

Clinically significant anxiety is very frequent following mTBI, as it was also observed in studies including the whole spectrum of TBI severity (Hammond et al., 2019). When measured with the HADS, we found that about 30% of our sample had symptoms of anxiety which could be considered clinically significant, a figure very similar to that reported by Vikane, Frøyland,

Næss, Aßmus, and Skouen (2019) who also used the HADS. Several factors have been proposed to explain the increase in anxiety following mTBI. For example, the circumstances of the accident, experiencing transport to the emergency room or hospital, and the hospital visit *per se* may can bring about anxiety in certain individuals (Moore et al., 2006). Furthermore, potential physical limitations, pain (i.e. headaches or neck pain), cognitive difficulties (i.e. difficulties with concentration) or behavioral changes (i.e. irritability) resulting from the injury could also be anxiety-provoking and limit a person's ability to return to work (Stergiou-Kita, Mansfield, Sokoloff, & Colantonio, 2016), and participate in social or leisure activities (Wise et al., 2010). The feeling of not functioning exactly quite "*like before*" can in itself be a source of significant anxiety. Many individuals having suffered mTBI report subtle sequelae unnoticeable to others which can nonetheless prevent them from accomplishing their daily tasks satisfactorily or impact their social roles and relationships. Having a serious injury might, in itself, be sufficient to increase the risk of suffering from anxiety, in fact a recent systematic review indicates that 11% to 56% of individuals who have sustained orthopedic trauma suffer from some form of anxiety symptoms up to 10 years after the injury (Breazeale, Conley, Gaiser, & Redeker, 2021). Pain, depression and PTSD are also common after musculoskeletal trauma (Kang, Ciminero, Parry, & Mauffrey, 2021). Future research could investigate the qualitative nature of anxiety sources after mTBI specifically, as well as common factors shared with other types of physical injuries. It would be important to examine to what extent persons who sustain mTBI experiences fear of having another head injury, and worries they might have about potential long-term consequences of the injury such as fear of long-term fatigue or cognitive issues, or fear of increased vulnerability to neurocognitive disorders (e.g. dementia).

Although symptom severity (measured with the HADS-A continuous score) remained relatively stable in the whole sample across evaluation time points, there was however a

significant reduction in the proportion of full-blown anxiety disorders between 4 and 12 months. Our results are in line with those Osborn, Mathias, Fairweather-Schmidt, and Anstey (2017), and indicate that the first few months after mTBI (up to 8 months according to our data) probably represent a period of increased vulnerability to anxiety. The prevalence of PTSD at 4 months following mTBI was 6.1% which is quite lower than the rate of 15.6% found in the meta-analysis of Van Praag, Cnossen, Polinder, Wilson, and Maas (2019). The prevalence rates of other anxiety disorders in the current study at 4 months post-mTBI (social phobia = 2%; panic disorder = 2.9%; generalized anxiety disorder = 0%; obsessive-compulsive disorder = 1%) were also below that found at 3 months post-mTBI by Meares et al. (2011), which were respectively 3.6%, 10.7%, 10.7% and 7.1%. Our quite conservative approach to establishing diagnoses could explain part of these divergences but also potentially our inclusion of non-specific disorders. Indeed, at 4-months post injury, we found high rates of mixed anxiety-depression disorder and of adjustment disorder (with anxiety features). In turn, at 8 and 12 months, generalized anxiety disorder became the most frequent disorder. It could be hypothesized that, for some individuals, the non-specific disorders or symptoms emerging in the first four months might represent prodromes of more pervasive forms of anxiety such as generalized anxiety disorder. Longitudinal studies extending well beyond the first year post-injury are needed to understand further how anxiety symptoms and disorders evolve in the longer term.

Regardless of time post-injury, the proportion of post-mTBI anxiety disorders and the severity of symptoms were significantly higher in participants with a history of anxiety disorders pre-injury. The presence of a pre-accident anxiety disorder consequently has an important role to play in the presence of anxiety after mTBI. These results are in line with those of several other teams (Gould et al., 2011; Karr, Iverson, Huang, Silverberg, & Yang, 2019; Vikane et al., 2019) who identified that persons with an anxiety disorder before TBI are significantly more likely to

suffer from an anxiety disorder after the accident than those who have never experienced an anxiety disorder in their lifetime. As Ponsford et al. (2012) suggest, it is possible that people who were vulnerable to anxiety before the accident have less effective coping strategies to deal with the stress and potential difficulties brought about by mTBI. Another hypothesis is that individuals who already had an increased sensitivity to anxiety pay more attention to the physiological or cognitive symptoms experienced after the accident, which in turn would cause more anxiety, establishing a vicious circle (Broshek, De Marco, & Freeman, 2015). Since it is expected that the majority of individuals will fully recover in the few weeks or months following mTBI, it is possible that persons with a history of anxiety worry more about their rate of recovery.

Personality traits and coping style are probably linked to post-mTBI adaptation and their role in anxiety-related conditions could be investigated in future studies. Neuropathological processes could also be at play, for example possible damage to the prefrontal cortex due to shearing forces of the frontal regions may increase vulnerability to anxiety (Ehlers & Clark, 2000; Kennedy, 2007; Landre, Poppe, Davis, Schmaus, & Hobbs, 2006), or to a reactivation of anxiety which was under control for some time (Moore et al., 2006).

We found that individuals who were anxious at 4 months post-mTBI presented with more symptoms of fatigue, irritability, perceived stress, cognitive difficulties, depression, insomnia and general pain 12 months after the accident, compared to persons who were not anxious at 4 months post-accident. Even if these results do not confirm any causal relationship, they corroborate other studies finding suggesting that anxiety may be a good predictor of persistent symptoms after the accident (Clarke et al., 2012; Cooper, Kennedy, Lu, & Reid, 2018; Dischinger et al., 2009; Meares et al., 2011; Snell et al., 2013). For example, in patients who were discharged from the ED after mTBI (but who were not hospitalised), de Koning and colleagues found that four months post-injury, 36% did not have a complete recovery as

measured with the Extended Glasgow Outcome Scale. Furthermore, patients who had scored above the cutoff on the HADS-Anxiety subscale two weeks after their injury had a three-fold risk of returning to an outpatient clinic with delayed recovery from their injury (de Koning et al., 2017). As Dischinger and colleagues propose, it is possible that the presence of anxiety after an accident exacerbates or prolongs the duration of certain TBI-related symptoms, for example by lowering the threshold for pain or through cognitive process such as maintaining concerns or fostering increased attention to physical sensations or cognitive functioning (Dischinger et al., 2009). Hence, the presence of anxiety in the first months following the accident could play an important role in the adjustment process and in the way individuals experience other frequent post-mTBI symptoms. Individuals having suffered a mTBI are often left to themselves in the first months after the accident, receiving little or no formal rehabilitation services, and must resume their activities without knowing quite what to expect, without knowing what the “*normal range*” of symptoms or exacerbation of symptom they should expect or be tolerating, creating much uncertainty. It is also possible that anxiety simply covaries with other symptoms in a cluster, for example headaches, fatigue, insomnia, irritability and depression. Future research could examine trajectories of multiple symptoms which present together following mTBI.

Our results suggest that it might be clinically relevant to systematically evaluate anxiety symptoms and disorders early-on after the accident, to monitor their evolution and to provide appropriate treatment, pharmacological and/or psychological, when necessary. This could allow for a reduction of anxiety and potentially other persistent symptoms. The present study underscores that individuals with a history of anxiety disorders should probably be followed-up even more closely. Broshek et al. (2015) found that a single psychoeducational session which informs about the frequent symptoms following mTBI and the expected evolution of recovery

helps to reduce symptoms in the first month after the accident. In this sense, informing individuals early on that the symptoms may take several months before fading, rather than a few days, as is commonly believed, may allow a reduction of anxiety. For persons requiring more sustained interventions, cognitive-behavioural therapy is known to be effective in reducing anxiety and depression symptoms in individuals with TBI (Hsieh et al., 2012; Potter & Brown, 2012). Tiersky et al. (2005) aimed to increase the use of effective coping strategies, reduce the level of stress, prevent relapse and help individuals with mTBI face the sense of loss of physical or cognitive abilities. Their intervention included psychoeducation, self-recording of thoughts, cognitive restructuring and behavioral exposure. They found that this treatment significantly improved emotional functioning, particularly by reducing anxiety and depression, compared to a wait-list control.

The results of the present study must be interpreted in the light of several limitations. Participants were hospitalised after their injury. As such, the results must be interpreted with caution and may not be applicable to individuals who were not hospitalised after mTBI. After mTBI, many individuals either visit the ED and are discharged home directly, others consult a primary care practitioner or another professional, and other still do not consult any professional. It is thus possible that our participants had an overall more severe accident (not necessarily a more severe brain injury however), leading to more consequences or injuries to other parts of the body. The latter could have influenced how they perceived their anxiety, overall functioning, symptoms, or recovery trajectory. Another limitation is that the evaluations included retrospective reports. A « *good-old days* » bias could have influenced the results, described as a tendency for persons with mTBI to under-estimate the frequency or severity of certain symptoms which may have been present before the accident (e.g. headaches, fatigue, inattentiveness) and over-estimate those present after the accident (Iverson, Lange, Brooks, & Lynn Ashton Rennison,

2010). Furthermore, our study did not identify which disorders were new-onset conditions vs conditions already present at the time of the accident. This should be investigated further in future studies. Certain diagnoses were not included in the assessment (i.e. anxiety disorder not otherwise specified, specific phobia) and as such it is possible that some cases were not detected. Although it is considered gold standard in neuropsychiatry to use diagnostic interviews based on the DSM, these interviews remain influenced by the interviewer's perceptions and a certain level of overlap can exist between different diagnostic categories. Given the longitudinal nature of this study, there is also a non-negligible proportion of missing data, but the GEEs are robust to this issue. The inclusion of a control group would also have widened the scope of the results, particularly by better characterising the specific effect of mTBI and that of the passing of time. Finally, the sample mainly represents francophone individuals from a mid-sized Canadian city (or nearby rural regions) where there is a good level of employment. As such, the sample may not represent mTBI cases seen in more dense and socioeconomically different urban centers where more assault or violence-related accidents may occur. Despite these limitations, the present study also has several strengths including consecutive recruitment, the use of well-validated measures of anxiety, a semi-structured diagnostic interview, and a relatively large sample size.

In conclusion, despite a reduction over time, the rates of anxiety in the first year after mTBI are elevated compared to the general population, with nearly one third of individuals having either an anxiety disorder or symptoms which can be considered clinically significant. Future research should examine the evolution of anxiety well beyond the first year following mTBI. Research is still very limited on the efficacy of preventive or therapeutic interventions to address anxiety in the first months post-mTBI. For example, it would be particularly informative to study the link between post-mTBI anxiety and variables such as anxiety sensitivity, tolerance

to uncertainty, tendency to catastrophize, social support, and cognitive fatigue or issues when returning to work. Future studies could also examine if persons having experienced multiple mTBIs are more at risk of anxiety disorders. For patients suffering from full blown anxiety disorders, ensuring access to adequate treatment, be it psychological or pharmacological therapies is, of course, essential.

Author contributions

All authors participated sufficiently in this research to warrant authorship and are in agreement with the content of the manuscript. GL, MCO, SBB, MJS, NL, JS, contributed to the conception and the design of this study. SBB, MG, GB and GS participated in the acquisition of data, analysis and interpretation of data. GL, GB, DT and GS drafted and revised the article. All authors reviewed the article critically and approved the final version.

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Table 1. *Socio-demographic and clinical characteristics (N = 120)*

	Participants <i>M (SD)</i>
Age (range: 18-65)	41.30 (14.3)
Length of hospital stay (range: 1-68)	11.62 (11.3)
First recorded Glasgow Coma scale score ^a (range: 10-15)	14.33 (0.9)
	<i>n (%)</i>
Uncomplicated mild TBI	53 (44.2%)
Complicated mild TBI	67 (55.8%)
History of previous mTBI	
None	87 (72.5%)
At least one	33 (27.5%)
Gender	
Male	91 (75.8 %)
Female	29 (24.2 %)
Education	
High school diploma or less	80 (66.7 %)
Higher than high school diploma	40 (33.3 %)
Married or partnered	
Pre-accident	74 (61.7 %)
Employment status pre-accident ^a	
Student	13 (10.8 %)
Employee	101 (82.8 %)
Retired	6 (5.3 %)
Temporary or permanent disability	8 (6.8 %)
Cause of the accident	
Motorized vehicle	53 (44.2 %)
Falls	47 (39.20 %)
Cycling, sports, recreation-related activities	5 (15.83 %)
Assault	3 (2.5%)
Other	3(2.5%)
History of anxiety disorder	
Negative	89 (79.50 %)
Positive	23 (20.50 %)

^a We report here the first GCS score available in the file (score may have rapidly risen). GCS scores for mild TBI are normally between 13 and 15. Four individuals had initial GCS scores between 10-12, probably due to substance use, but the medical file indicated a final diagnosis of mTBI. ^b Some participants could be both student and employee.

Table 2. *Prevalence of anxiety disorders on the MINI and severity of anxiety symptoms on the HADS-A according to measurement time-point.*

	Measurement time-point			
	Pre	4 months	8 months	12 months
Anxiety disorders on the MINI				
n (%)				
Generalized anxiety disorder	2 (1.8%)	0	6 (6.5%)	5 (5.6%)
Post-traumatic stress disorder	7 (6.5%)	6 (6.1%)	2 (2.2%)	4 (4.5%)
Panic disorder with agoraphobia	3 (2.7%)	2 (2.0%)	1 (1.1%)	1 (1.1%)
Panic disorder without agoraphobia	1 (0.9%)	2 (2.0%)	3 (3.3%)	1 (1.1%)
Agoraphobia without history of panic disorder	2 (1.8%)	3 (2.9%)	0	0
Social phobia	2 (1.8%)	2 (2.0%)	1 (1.1%)	1 (1.1%)
Obsessive-compulsive disorder	2 (1.8%)	1 (1.0%)	0	0
Adjustment disorder with depressed or anxiety-depressed mood	1 (0.9%)	6 (5.9%)	3 (3.3%)	0
Mixed anxiety-depression disorder	5 (4.5%)	10 (9.6%)	4 (4.3%)	2 (2.2%)
At least one anxiety disorder	23 (20.5%)	25 (23.8%)	14 (15.2%)	10 (11.2%)
Anxiety symptoms on HADS-A				
Average score (standard deviation)		6.13 (4.37)	5.88 (4.43)	5.47 (4.27)
Clinically significant symptoms (HADS-A \geq 8), n (%)		34 (36.2%)	27 (31.8%)	22 (27.80%)
At least one anxiety disorder or HADS-A \geq 8		47 (48.5%)	31 (37.8%)	25 (32.5%)

Notes. Percentages are calculated on all available data for each time point (N may vary slightly). A single individual can fulfill the diagnostic criteria of multiples disorders unless exclusion criteria are specified by the DSM-IV-TR (i.e. Adjustment disorder and Generalized anxiety disorder are mutually exclusive). Generalized Anxiety Disorder requires symptoms to be present for the past six months. HADS-A= Hospital Anxiety and Depression Scale- Anxiety subscale. MINI = Mini International Neuropsychiatric Interview.

Table 3. *Anxiety according to the presence or absence of a history of anxiety disorders*

History*	Measurement time-point			Statistic
	4 months % [IC 95%]	8 months % [IC 95%]	12 months % [IC 95%]	
Proportions of individuals with at least one anxiety disorder				Time Effect: $\chi^2 (2, N = 283) = 9.065, p = \mathbf{0.011}$
Negative	14 [7;21]	10 [4;17]	10 [4;17]	History Effect: $\chi^2 (1, N = 283) = 15.050, p < \mathbf{0.001}$
Positive	64 [44;85]	38 [16;59]	27 [5;48]	Interaction: $\chi^2 (2, N = 283) = 3.745, p = 0.154$
HADS-A score equal to or greater than 8				Time Effect: $\chi^2 (2, N = 241) = 1.234, p = 0.540$
Negative	33 [22;43]	21 [11;30]	21 [12;30]	History Effect: $\chi^2 (1, N = 241) = 16.876, p < \mathbf{0.001}$
Positive	68 [45;92]	77 [56;98]	69 [44;94]	Interaction: $\chi^2 (2, N = 241) = 1.870, p = 0.393$
Continuous score on HADS-A				Time Effect: $\chi^2 (2, N = 241) = 0.522, p = 0.770$
Negative	5.57 [4.57;6.57]	5.00 [4.06;5.94]	4.71 [3.84;5.57]	History Effect: $\chi^2 (1, N = 241) = 33.374, p < \mathbf{0.001}$
Positive	9.30 [7.46;11.15]	10.47 [8.44;12.51]	10.41 [8.47;12.35]	Interaction: $\chi^2 (2, N = 241) = 6.351, p = \mathbf{0.042}$

Note. The N corresponds to the number of observations, not to the number of participants included in the analysis.

*A positive history refers to the presence of at least one anxiety disorder pre-accident.

Table 4. Average scores for various symptoms at 12 months post-accident according to the presence ($HADS-A \geq 8$) or absence ($HADS-A < 8$) of significant anxiety 4 months after the injury

Dependant Variables	Scores at 12 months		<i>p</i> -value
	Non-anxious at 4 months M(SD)	Anxious at 4 months M(SD)	
Fatigue	9.94 (3.99)	13.08 (3.79)	p = 0.002
Anger/Irritability	5.78 (1.76)	8.17 (3.17)	p < 0.001
Stress	10.71 (6.37)	18.67 (7.37)	p < 0.001
Depressive symptoms	2.16 (2.55)	5.83 (4.41)	p < 0.001
Sleep difficulties	6.54 (5.30)	14.58 (5.94)	p < 0.001
Pain ^a	68.41 (23.45)	44.91 (25.90)	p < 0.001
Cognition ^a	73.14 (20.66)	61.25 (20.34)	p = 0.022

Note. ^aA lower score indicates a higher intensity of symptoms or worse functioning.