Brain Connectivity and Behaviour in Post-Concussion Syndrome: A Scoping Review Protocol

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Abstract

Background About 10-15% of patients experience persistent symptoms 3-months post-concussion, referred to as Post-Concussion Syndrome (PCS). There are no biomarkers for detecting this condition, but advanced neuroimaging tools such as Diffusion Tensor/Weighted Imaging (DTI/DWI) or functional MRI (fMRI) can detect subtle changes in the integrity of white matter tracts or brain activity, respectively. Methods This study protocol presents search strategies for a scoping review that provides an overview of the studies that assessed both alterations of structural and/or functional connectivity and cognitive/neuropsychiatric outcomes in PCS. Discussion A better understanding of the brain-behaviour relationships in PCS can lead to improved diagnosis of this condition. Scoping Review Protocol Registration: osf.io/sqt7d

1. Background

Every year, 69 million people worldwide are estimated to suffer from a Traumatic Brain Injury (TBI) with approximately 80% of these cases diagnosed as a mild TBI (mTBI), defined as scoring 13–15 on Glasgow Coma Scale (GCS).[1,2] The actual prevalence is difficult to determine as many individuals with mTBI or concussion, do not seek medical attention.[3,4] Some authors use mTBI and concussion interchangeably while others refer to concussion as reversible pathological changes with most victims scoring 15 out of 15 on the GCS.[5–7] These terms are used synonymously here to capture a broader range of articles in the literature.

Although most people who have experienced a concussion recover within weeks to months, in 10–15% of patients, symptoms including physical (e.g., headache, dizziness, fatigue), cognitive (e.g., memory issues, difficulty concentrating) and emotional (e.g., anxiety, depression) may persist longer than 3 months, which is referred to as Post-Concussion Syndrome (PCS).[8–10] The 2016 Berlin Consensus Statement on Concussion in Sport defines persistent post-concussive symptoms as having complaints longer than normal recovery time, which is estimated to be 10–14 days in adults and 4 weeks in children.[5] This is mostly accepted in literature related to contact sports. On the other hand, clinical criteria for diagnosing PCS were first proposed in 1992 in the International Classification of Diseases, Tenth Revision (ICD–10)[11], and these criteria were later adapted and modified in the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV).[12] ICD–10 clinical criteria require a history of TBI and the presence of three or more of the following eight symptoms: 1) headache, 2) dizziness, 3) fatigue, 4) irritability, 5) insomnia, 6) concentration or 7) memory difficulty, and 8) intolerance of stress, emotion, or alcohol.[11] Alternatively, DSM-IV describes PCS as experiencing objective impairment in memory or attention with three of the following symptoms: headache, fatigue, sleep disturbance, dizziness, irritability, affective disturbance, personality change, apathy, anxiety or depression, for more than 3 months.[12] Since many articles do not use DSM-IV or ICD–10 for assessing post-concussive symptoms, we extend our literature search to the studies with patients experiencing persistent symptoms 1 month post-injury based on other assessments such as Rivermead Post-Concussion Symptom Questionnaire.[13]

The symptoms listed above are, unfortunately, not specific to PCS, further complicating its diagnosis. Moreover, brains of patients with PCS often appear normal on conventional Computed Tomography (CT) and Magnetic Resonance Imaging (MRI) scans. The challenge is to develop and utilize more sensitive imaging tools to detect subtle changes in the structure or the functional connectivity within the brain to better understand the neuropsychiatric and behavioural outcomes. One promising biomarker could be the alterations of white matter tracts that transport information in the brain, detected with Diffusion Tensor or Weighted Imaging (DTI, DWI).[14,15] The literature suggests a link between disruption of white matter integrity in patients experiencing post-concussive symptoms and neuropsychological deficits such as greater aggression[16] and cognitive impairment[17]. Another potential biomarker for PCS involves the disruption of functional connectivity (i.e. interaction and activation) of various brain regions. Functional MRI (fMRI) allows us to investigate the alterations in the intrinsic connectivity of brain regions while the person is actively involved in a task or at rest[18]. Alterations in resting state functional connectivity in patients with mTBI related persistent symptoms have been correlated with symptom severity.[19,20]

Although these studies increase our understanding of the brain-behaviour relationship in PCS, they often report very distinct or even conflicting findings on DTI/DWI or fMRI parameters or the brain regions that are part of disrupted structural or functional brain networks. Such differences in findings may arise from many factors including the variability in recruitment sites (i.e. military, contact sports), patient population (i.e. age, sex, education levels), tests administered for assessing symptom severity or neuropsychiatric/cognitive deficits, and techniques used for processing neuroimages. It is necessary to contextualize, evaluate and summarize the existing findings to address the gap in the field of PCS, and provide guidance for researchers and clinicians.

There have been numerous systematic and scoping reviews on brain network disruptions in concussion/mTBI measured with DWI/DTI and fMRI techniques. A very detailed review by Shenton *et al.*[21] reported a great deal of variability in DTI findings in mTBI research including the location of structural and functional connectivity alterations and the degree of these alterations measured with different metrics (i.e. Fractional Anisotropy, Medial Diffusivity). This review suggests that diffusion imaging techniques are promising for revealing subtle changes in the brain after mTBI; however, behavioural correlates of these brain changes were not investigated.[21] A review by McDonald *et al*[22] suggested that fMRI evaluating the brain function, either at rest or during a specific task, can provide an objective way to link the functional connectivity changes in particular brain regions to cognitive/behavioural outcomes or mTBI-related symptomatology. A recent scoping review estimated that 58% of these patients develop some sort of cognitive impairment, a much larger number than usually reported.[23] According to the commentary by Iverson *et al*[24], not every patient experiences the same persistent symptoms to the same degree. There have been few reviews summarizing existing literature on structural and functional changes along with behavioural outcomes, including cognitive impairments, neuropsychiatric deficits or symptomology, in patients with persisting post-concussive symptoms. Khong *et al.*[25], reported that loss of integrity in long white matter tracts such as corpus callosum was the most

cited abnormality in PCS literature, which was consistent with a previous review.[17] The current literature in PCS is limited because of a lack of converging knowledge due to few studies published on the topic.[25]

As described, most of the knowledge synthesis in the field has focused on only one domain: loss of white matter integrity, disruption of functional connectivity or symptoms/behavioural deficits observed in patients with PCS. To our knowledge, there is no systematic summary of literature focused on understanding the structural or functional changes along with cognitive, neuropsychiatric measures or symptom severity in the adult population with PCS. In this paper, we provide a protocol for a scoping review that will summarize and synthesize the literature on both structural and functional connectivity changes and cognitive, neuropsychiatric measures or symptom severity in patients with PCS. We specifically target the studies that utilized DTI/DWI and resting state or task-based fMRI for detecting alterations in white matter integrity and functional connectivity in PCS patients, respectively. The objective of our scoping review is to provide an overview of the literature on the brain-behaviour relationship in patients with PCS, specifically using the neuroimaging tools mentioned above. The usage of highly variable terminology has led to confusion, not only in the diagnosis or detection of PCS, but also difficulty in finding relevant literature in this field. Thus, this scoping review will inform future studies that aim to find neuroimaging biomarkers for PCS while providing an approach for an effective search of the relevant literature.

2. Methods / Design

Our methodology for the scoping review will follow the Joanna Briggs Institute (JBI) Reviewer's Manual for scoping reviews with a six-stage framework.[26] The JBI guidelines are based on previous work by Arksey and O'Malley[27] and Levac *et al.*[28] This framework includes 6 steps; identifying the research question, finding relevant studies, selecting the relevant studies, extracting data, summarizing/reporting the results and an optional step of consulting the stakeholders that is not applicable to this review. The results of our scoping review will be reported in accordance with Preferred Reporting Items for Systematic Reviews and Meta-Analysis Extension for Scoping Reviews (PRISMA-ScR).[29]

2.1. Literature Search Strategy

We will search Medline (Ovid), Embase (Ovid) and PsycINFO (Ovid) databases for primary research articles published between 1 January 1966 and 5 February 2020 for our scoping review. As indicated in our protocol, this initial date was chosen because one of the first formal definitions of concussion was proposed in 1966 by the Committee to Study Head Injury Nomenclature.[30] Our search terms have been optimized to target articles that included the following 3 domains (Figure 1, Table 2): 1) adult patients with PCS or concussion/mTBI related symptoms persisting more than a month, 2) neuroimaging techniques, specifically DTI/DWI or fMRI, for studying structural and functional connectivity, respectively and 3) cognitive, neuropsychiatric or symptom assessments (Figure 1). We optimized our search terms with the following strategy: 1) we selected 10 articles that are eligible for our scoping review, 2) we

developed the search terms based on the first 5 of these articles, 3) these initial search terms were then tested and updated until the other 5 articles appeared in our search.

Based on JBI Reviewer's Manual for scoping review, a second search strategy will involve backward snowballing. The complete reference list of the articles that are identified to be included in the scoping review will be searched and imported using Scopus. These additional articles will be then included in our screening procedure.

2.2. Eligibility Criteria

Study eligibility criteria were developed to target studies that included adults with age range of 16–65 with PCS and the diagnosis of PCS was primarily based on DSM-IV and ICD–10 (Table 1). Since very few studies use these diagnostic criteria for persisting post-concussive symptoms, we extended our inclusion criteria to the studies on individuals experiencing persistent symptoms at least one month after the injury. In addition to the articles that defined concussion as GCS of 15, we extended our inclusion criteria to the articles in the mTBI literature. Although it was not explicitly stated in out inclusion criteria (Table 1), the definition of mTBI includes a score of 13–15 on GCS, less than a day long post-traumatic amnesia (PTA), less than one hour of loss of consciousness (LOC) with slight variations in such measures reported by various research groups.[31,32]

Eligible studies must employ neuroimaging tools such as DTI/DWI or resting-state/task-based fMRI for measuring the change in white matter integrity and functional connectivity, respectively. Thus, DTI/DWI and fMRI parameters and brain regions or networks reported to be disrupted will be our primary outcome. As the secondary outcome, the eligible studies must also include behavioural outcomes of PCS patients including symptom reports (i.e. measured with Rivermead Post-Concussion Symptom Questionnaire[13] or the Post-Concussion Symptom Scale[33]), or neuropsychiatric assessments (i.e. Personality Assessment Inventory[34]), or cognitive tests (i.e. The Stroop Color and Word Test[35]).

2.3. Data Management and Screening

The complete reference for the identified articles from databases, based on the inclusion/exclusion criteria mentioned above, will be saved as.ris files to be uploaded onto Covidence.[36] First, the two reviewers (MG and AS) will screen the title and abstract of each paper, independently, based on the eligibility criteria outlined above. Second, the two independent reviewers will screen full text of each study identified in the first step. Following the completion of the initial search and screening, the articles obtained from backward snowballing will be saved as.ris files on Scopus and uploaded to Covidence. The two reviewers will then independently conduct title-abstract and full-text screening of these additional articles.

2.4. Data Extraction

The study team will create the data extraction forms to identify the data items, provided in Table 3, from each study. Before starting the extraction process, the two reviewers (MG and AS), that will undertake the screening process, will test the created forms and necessary items by extracting data from five initial papers together. Once the data extraction tools are confirmed, the reviewers will continue the process, extracting data from each identified study, independently. At the end, to check consistency of the process, the reviewers will compare the extracted information and resolve the discrepancies with a third party (MCT).

2.5. Data Synthesis

It is not possible to conduct a meta-analysis due to the nature of our question. We are not specifying a particular brain region or behavioural outcome that may be associated with PCS as there is great variation in findings in the literature. We are instead interested in mapping the literature on this topic. Based on recent guidelines, this review will be written in a narrative style to speak about the correlations that have been reported on the structural/functional changes, measured with DWI/DTI and fMRI, and behavioural outcomes, including neuropsychiatric/cognitive assessments or symptom severity.

3. Discussion

There are very few reviews summarizing existing literature on structural and functional changes and their relationship to behavioural outcomes, including cognitive impairments and neuropsychiatric symptoms in PCS patients. The proposed review aims to summarize the literature and identify the gaps in the field to inform future research. A better understanding of the brain-behaviour relationship in patients with PCS would facilitate development of better diagnostic measures, which could accelerate targeted treatments for this condition.

List Of Abbreviations

Mild TBI (mTBI); Glasgow Coma Scale (GCS); Post-Concussion Syndrome (PCS); International Classification of Diseases, Tenth Revision (ICD-10); Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV); Computed Tomography (CT); Magnetic Resonance Imaging (MRI); Diffusion Tensor Imaging (DTI); Diffusion Weighted Imaging (DWI); Functional MRI (fMRI); Joanna Briggs Institute (JBI).

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

All authors have seen and reviewed the contents of this manuscript and consent for publication.

Availability of data and materials

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Competing interests

There are no competing interests to declare.

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Author contributions

MG and AS created the study protocol, developed the search strategy while MCT provided input throughout this process. The first draft of the manuscript for the protocol was written by MG. The figures and tables were created by AS. The manuscript was revised, edited and approved by MCT.

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Figures

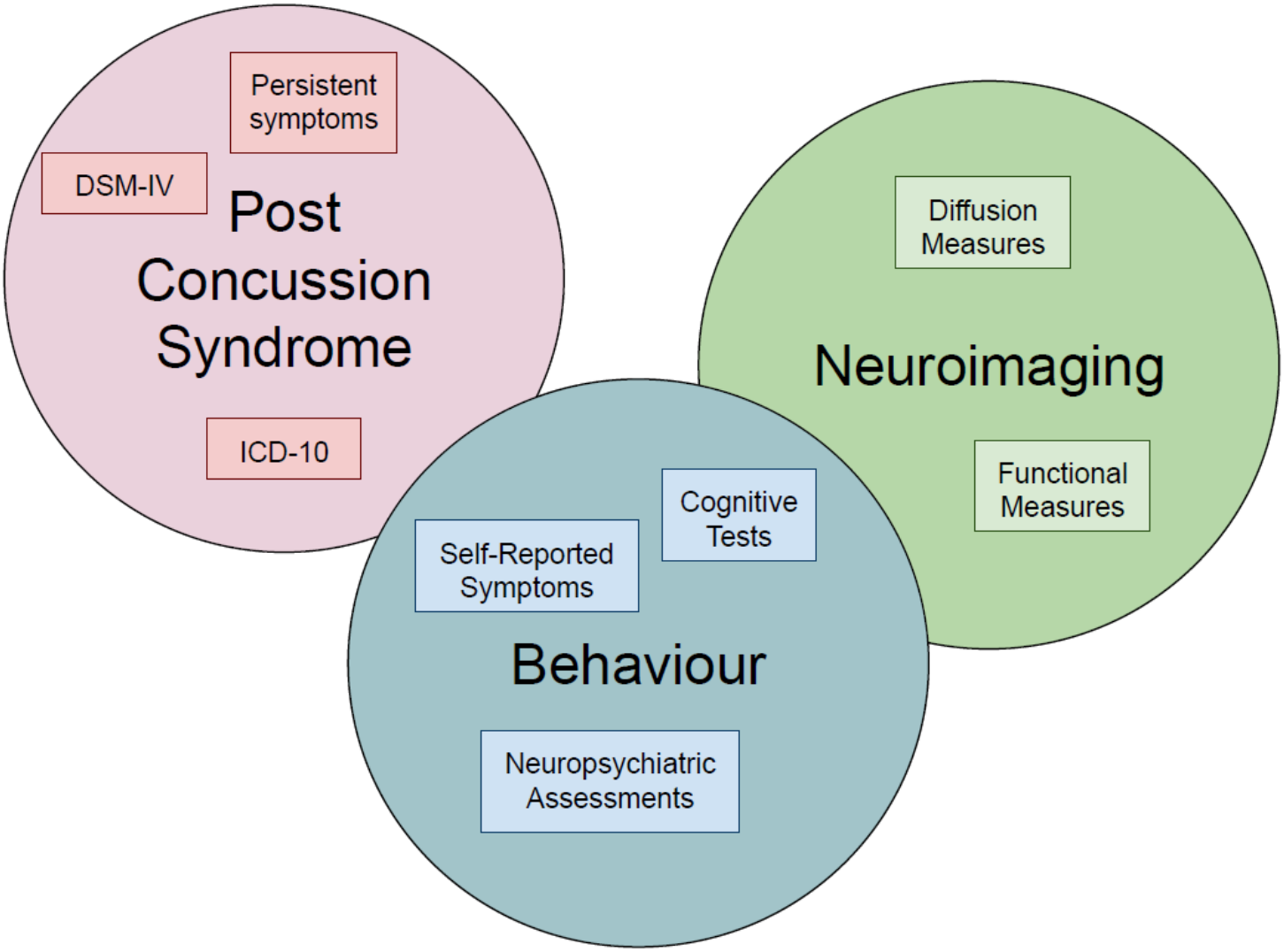

Figure 1

The main domains the screened articles must include.

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