

INPLASY

Uncovering the relationships between fatigue, sleep, and cognition after an Acquired Brain Injury: A systematic review protocol

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ADMINISTRATIVE INFORMATION

Support - The University of Western Australia.

Review Stage at time of this submission - Preliminary searches.

Conflicts of interest - None declared.

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Amendments - This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 1 October 2024 and was last updated on 5 November 2024.

INTRODUCTION

Review question / Objective This review will aim to understand the various associations between mental fatigue, sleep disturbances, and cognitive impairment in adults with acquired brain injury (ABI) through a systematic review. Specifically, the review will focus on the following objectives: (1) to identify specific cognitive domains that significantly contribute to trait fatigue and (2) to determine whether sleep disturbance is a possible mediator or moderator between cognitive impairment and trait fatigue.

Rationale Previous studies have hypothesised that trait fatigue results from the compensatory efforts required by individuals with an ABI to meet everyday demands in the presence of decreased cognitive capacity (Van Zomeren & Van den Burg, 1985; Ponsford et al., 2012). A recent systematic review and meta-analysis concluded that the association between global cognitive impairment

and fatigue was weak (Dillon et al., 2023). Instead, it was suggested that domain-specific cognitive impairments, including attention, processing speed, and working memory, were found to be significant contributors to fatigue (Johansson et al., 2009; Jonasson et al., 2018). However, data on the specific cognitive domains that significantly contribute to trait fatigue – attention, processing speed, and working memory – are limited. Furthermore, the current literature is limited to a few individual studies and theses, each employing diverse methodologies that measure several confounding cognitive processes alongside the domain under investigation (Dillon et al., 2023). Thus, further review of the available research is necessary to clarify the mechanisms driving fatigue in individuals post-ABI. Consequently, this systematic review aims to explore the mechanisms between mental fatigue, sleep disturbances, and domain-specific cognitive impairment. In particular, it firstly aims to characterise specific cognitive domains that significantly correlate to trait fatigue. This review can potentially consolidate and

synthesise existing studies, providing a clearer picture of the cognitive domains that affect mental fatigue.

Regarding sleep difficulties in the context of brain injury, few studies have attempted to investigate the relationship between fatigue, sleep impairment, and fatigue. One particular study concluded that fatigue was linked to slowed information processing and increased mental effort, with self-reported sleep disturbances contributing to the fatigue experience (Ponsford et al., 2012). However, as the fatigue experience is multifactorial and complex, the direction of causality in the relationship of the factors associated with fatigue is not fully understood. Thus, the current systematic review secondarily aims to examine the role of sleep disturbance as a possible mediator or moderator between cognitive impairment and fatigue in the adult ABI population. Understanding the interrelationships surrounding fatigue can inform functional outcomes and target rehabilitation strategies for individuals with brain injury and chronic fatigue symptoms (Prigatano, 1999).

Condition being studied This review aims to comprehensively explore the interrelationships between fatigue, sleep disturbances, and cognitive impairment in adults with ABI. ABI refers to the damage to brain functioning attributed to non-neurodegenerative causes (Teasell et al., 2007). ABI may typically lead to diverse brain changes that disrupt cognitive functioning in various domains, such as attention and memory networks (Povlishock, 1991). These neural disruptions can also lead to cognitive, emotional, and behavioural deficits. Fatigue and sleep disturbances, for instance, are among the most common consequences of brain injury across the spectrum of injury severity (Ponsford & Sinclair, 2014).

Fatigue is a universal experience in both healthy and brain-injured individuals, characterised by feelings of exhaustion and lack of energy (Yoon et al., 2023). Up to 80% of patients with brain injury are significantly affected by fatigue, regardless of injury severity (Mollayeva et al., 2014). The current fatigue literature is categorised into mental and physical fatigue. Mental fatigue can be broken down further into trait fatigue – the prolonged experience of fatigue unaffected by task demands – and state fatigue – the momentary experience of fatigue that is generally influenced by present demands (Kluger et al., 2013). Trait fatigue levels are intimately linked to the progression of depression, sleep, pain, and cognitive difficulties, which adds to the core fatigue related to neurological insult (Beaulieu-Bonneau & Ouellet, 2017).

Sleep disturbances associated with brain injury include formally diagnosed sleep disorders, such as insomnia and hypersomnia, and specific complaints, such as the quality, quantity, and duration of sleep (O’Sullivan et al., 2015; Theadom et al., 2015). About 30-70% of brain-injured individuals continue to report sleep disturbances beyond the acute recovery period (Orff et al., 2009), which may subsequently increase trait fatigue (Ponsford et al., 2012). Sleep disturbances may potentially lead to impaired functioning ability and reduced quality of life due to their associated cognitive, affective, and fatigue impairments (Lowe et al., 2020). It is postulated that disturbed sleep may be due to the direct effects of brain injury (Sinclair et al., 2014), as well as fatigue and depression after ABI, or medication side effects. While the causality of sleep disturbances after a brain injury remains unclear and likely multifactorial, it plays a critical role in the ABI recovery process.

Up to 70% of individuals following brain injury exhibit some cognitive difficulties (Lagogianni et al., 2018). These cognitive changes tend to occur in the domains of processing speed, attention, memory, and executive functioning (Åkerlund et al., 2021). Previous studies have found that deficits in the cognitive domains of working memory, attention, and processing speed, were associated with worsened trait fatigue (Dillon et al., 2023). Conversely, sleep disruption post-ABI and mental fatigue (Cronin & O’Loughlin, 2018) were found to predict reduced cognitive performance in certain tasks.

METHODS

Search strategy The review will align with the Preferred Reported Items for Systematic Reviews and Meta-Analyses guidelines (PRISMA; Page et al., 2021). A comprehensive search of the literature will be completed through the use of the following online databases: MEDLINE, PsycINFO, ScienceDirect, Scopus, EMBASE, Web of Science, and CINHALL. Additional records will be identified and supplemented through hand-searching the reference lists of included articles. Studies that examine mental fatigue in an ABI sample and use cognitive and sleep measures will be included. Searches will be re-run prior to the final analyses and any additional identified studies will be included.

Concept 1: ((head OR brain OR crani* OR cerebr* OR cerebell*) ADJ2 (injur* OR incident* OR trauma* OR damage* OR accident* OR hemorrhag* OR infarct* OR ischemi* OR thrombo* OR emboli* OR occlus* OR contusion)) OR concussi* OR “post-

concussi** OR stroke* OR hematoma* OR "diffuse axonal injur**" OR "tumor resection" OR "tumour resection" OR "aneurysm" OR hypoxia OR "traumatic brain injury" OR "acquired brain injury" OR TBI OR ABD OR ABI)

Concept 2: (fatigue OR tiredness OR slowness OR weariness OR exhaustion OR "lack of energy" OR lethargy OR apathy)

Concept 3: (sleep OR "sleep disorders" OR "sleep wake disorders" OR "sleep disturbance*" OR insomnia OR hypersomnia)

Concept 4: (cogniti* OR memory OR "working memory" OR attention OR vigilance OR concentration OR "executive function" OR speed OR processing OR information).

Participant or population This review will only include studies with an adult population (16 – 70 years old) with an ABI. ABI is comprised of traumatic brain injury (TBI) and non-TBI including aneurysm, stroke, brain tumour and hypoxia. Full inclusion and exclusion criteria are listed below.

Intervention Not applicable.

Comparator As most studies focusing on fatigue within the brain injury population predominately employ a within-subjects design, this review will not include a comparator group. Comparative intervention studies will not be within the scope of this review, as our primary objective will be looking at the relationships between fatigue, sleep, and cognition after a brain injury.

Study designs to be included This review will include studies that have at least one time point. Therefore, the review will include cross-sectional, longitudinal, cross-sectional, and case studies. Studies that will be excluded are animal studies.

Eligibility criteria The inclusion criteria for the studies selected will be limited to a) studies published in the English language, b) studies that use an adult population (16-70 years old), c) studies that use published measures of fatigue, cognition, and sleep, and d) inclusion of ABI diagnosis with acute onset of injury for participants. In particular, ABI is comprised of traumatic brain injury (TBI) and non-TBI including aneurysm, stroke, brain tumour, and hypoxia. Studies on moderate-to-severe or mixed TBI severity will be included. We will consider all quantitative study designs with a focus on the relationship between mental fatigue, sleep disturbances, and cognitive impairment for adults after brain injury. However, priority will be given to experimental studies that are peer-reviewed articles with full-texts available.

Studies will be excluded if a) the sample includes participants with neurodegenerative diseases (i.e., dementia) or neurodevelopmental disorders, b) the study solely focuses on treatment or intervention, and c) the sample only includes participants with mild TBI severity.

Information sources The review will align with the Preferred Reported Items for Systematic Reviews and Meta-Analyses guidelines (PRISMA; Page et al., 2021). A comprehensive search of the literature will be completed through the use of the following online databases: MEDLINE, PsycINFO, ScienceDirect, Scopus, EMBASE, Web of Science, and CINHALL. Similarly targeted searches will be performed for grey literature in the following databases: ProQuest Dissertations & Theses Global, Open Grey, Grey Net International, and Grey Matters. Additional records will be identified and supplemented through hand-searching the reference lists of included articles. Studies that examine mental fatigue in an ABI sample and use cognitive and sleep measures will be included. Searches will be re-run prior to the final analyses and any additional identified studies will be included.

Main outcome(s) Correlations between fatigue, sleep disturbances, and cognition, as measured by published measures, such as questionnaires, assessments, or physiological measures.

Additional outcome(s) Sample age, sex, education, premorbid psychiatric history, injury severity and time since injury.

Data management The data will be collected in a three-step process outlined by Peters et al. (2015) – a preliminary limited search, a second search across all included databases, and reference searching.

An initial limited search on MEDLINE and PsycINFO will be done, and an analysis of the text words contained in the title, abstract, and index terms of retrieved articles. The key concepts utilised include acquired brain injury, fatigue, sleep disturbances, and cognitive impairment. To ensure that studies were relevant in answering the review questions, the meaning of the key concepts in the review question were clarified while appropriate search terms will be generated.

A second search using all identified keywords and index terms will be undertaken across all included databases. All stages of data screening and extraction will be managed using Covidence software. After completing the database searches, the titles, authors, years of publication, and abstracts will be downloaded and extracted. Once

duplicates are removed, the lead author will screen titles and abstracts against the outlined inclusion and exclusion criteria. The titles and abstracts will be sorted into a “retain”, “unclear”, and “discard” folder. Full-text screening will then occur for the remaining “retain” and “unclear” articles, subsequently re-categorising them into the “retain” or “discard” folder. Similar procedures will be conducted for the various databases of grey literature.

Once all included articles from the database and grey literature search are concluded, additional records will be identified and supplemented through the reference lists of included articles, until no new studies meet the inclusion criteria. The search will be conducted from the inception of each included database to the present.

A second author will impartially screen 30% of the articles for inclusion in the review at each stage of the screening process to ensure credibility. Exclusion reasons and the level of agreement between the two authors will be recorded. The research team will assess decisions and any disagreements regarding judgments will be resolved.

All extracted data will be stored and managed electronically using reference management software (Covidence, EndNote) and Microsoft Excel. This will facilitate efficient organisation and retrieval of data throughout the review process. The data will be manually obtained by the lead author and checked by a second author. Authors will be contacted to obtain missing data or clarify any uncertainties. The quality of the final selected studies will be examined according to the Joanna Briggs Institute Critical Appraisal Tools (Aromataris et al., 2015). Extracted data will include:

- Study title, author, journal, location, and year of publication
- Aim of study
- Study funding sources and reported conflicts of interest
- Participant recruitment method and setting
- Sample demographics including age, gender compositions, educational history, premorbid medical history (if any)
- Brain injury characteristics, including injury type, severity and time since injury
- Published measures of fatigue, cognition, and sleep used in the study
- Statistical analysis techniques
- Results.

Quality assessment / Risk of bias analysis The quality of the final selected studies will be examined according to the Joanna Briggs Institute Critical Appraisal Tools (Aromataris et al., 2015).

Strategy of data synthesis The review will present a comprehensive qualitative synthesis of its findings. Characteristics of the included papers and a descriptive summary of their findings will be summarised. The systematic review will shed light on the significant domain-specific cognitive impairments following a brain injury. Furthermore, the review will examine the possibility of sleep disturbances as a mediating or moderating factor between cognitive impairment and fatigue.

Subgroup analysis Not applicable.

Sensitivity analysis Not applicable.

Language restriction English Language only.

Country(ies) involved Australia.

Keywords Acquired brain injury; trait fatigue; sleep disturbances; cognitive impairment; systematic review; neuropsychology.

Dissemination plans The author will aim to publish the results in a peer-reviewed journal article.

Contributions of each author

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Contributions: Conceptualisation of the review, literature search, article screening, development of the selection criteria and risk of bias assessment strategy, data extraction, quality assessment, initial draft of manuscript and approval of final manuscript.

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