A novel integrated perspective linking physiological and psychological consequences of mild traumatic brain injury.

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Primary Objective: - To investigate whether or not persistent complaints and poor outcome after mTBI be explained by an interaction between physiological and psychological factors.Secondary Objective(s): - To identify specific patterns of brain…

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Structural brain disorders
Study type	Observational invasive

Summary

ID

NL-OMON50090

Source
ToetsingOnline

Brief title
AIM-TBI

Condition

- Structural brain disorders
- Cognitive and attention disorders and disturbances

Synonym
concussion; headtrauma.

Research involving
Human

Sponsors and support

Primary sponsor: Universitair Medisch Centrum Groningen
Source(s) of monetary or material Support: Ministerie van OC&W

Intervention

Keyword: Mild traumatic brain injury, Physiology, Post-traumatic complaints, Psychology

Outcome measures

Primary outcome

- Post-traumatic complaints (measured using the head injury symptom checklist

(HISC) at 6 months post-injury).

- Glasgow Outcome Scale Extended (GOSE) at 6 months post-injury.

Secondary outcome

Secondary parameters:

- Blood cytokine levels at the ED and at 4-6 weeks post-injury.

- Blood biomarker levels (proteins of cell injury) at the ED.

- Salivary cortisol levels at the ED.

- Hair cortisol levels at 4-6 weeks post-injury.

- Heartrate variability at the ED.

- EEG at the ED, and at 4-6 weeks post-injury.

- Brain network connectivity at 4-6 weeks post-injury.

- HISC at 2 weeks post-injury.

- Anxiety/depression at 2 weeks post-injury (Hospital Anxiety and Depression

Scale (HADS)).

- Coping (Utrechtse Coping List (UCL) at 2 weeks post-injury).

- Personality characteristics (Big Five Inventory (BFI) at 2 weeks post-injury).

Other parameters:

- Baseline parameters (age, sex, educational level, pre-injury working status,

injury characteristics, CT-abnormalities, acute complaints).

- Pre-injury mental health state and stress.

- Lifestyle factors (alcohol and caffeine consumption, tobacco use, exercise).

Study description

Background summary

Mild traumatic brain injury (mTBI) is the most common neurologic disorder. One out of 4 patients develops long-lasting cognitive and emotional complaints that interfere with daily functioning. Therefore, mTBI poses a significant public health burden. Over the years multifactorial models have been developed, which aid in the prediction of outcome after mTBI. It has been shown that in addition to acute injury related factors, such as loss of consciousness and amnesia, outcome is strongly influenced by pre-existent psychological factors, for instance coping style and emotion regulation. Despite these scientific efforts, persistent complaints are still rather unpredictable in individual patients, for whom injury mechanisms are often comparable.
So far, little is known about the influence of physiological effects of the injury, such as cellular injury, neuroinflammation, and acute stress, on outcome after mTBI. Previous functional MRI (fMRI) research has demonstrated that persistent complaints after mTBI are related to alterations in neural networks. Therefore, a pivotal question is whether acute physiological effects lead to disturbances in neural networks that are important for emotion regulation, and if there is an interaction with pre-existent personality, coping style, and stress levels, This topic has never been touched upon, and therefore forms a gap in mTBI research.
With the current study, we aim to conduct biochemical, psychometric, MRI- and EEG-experiments in order to disentangle the interaction(s) between (acute) physiological and (long-term) psychological consequences of TBI. Hopefully, this will lead to a better understanding of the etiology of persistent complaints and poor outcome, and to starting points for the development of tailored pharmacological and/or psychological treatments for patients with mTBI.

Study objective

Primary Objective:
- To investigate whether or not persistent complaints and poor outcome after mTBI be explained by an interaction between physiological and psychological factors.

Secondary Objective(s):
- To identify specific patterns of brain specific protein, cortisol and cytokine release and HRV in patients with mTBI.
- To determine if cortisol and cytokine release in patients with mTBI differ from patients with another stressful condition (i.e. orthopedic injury), and healthy controls.
- To find possible relationships between acute physiological disturbances (inflammation, stress) in mTBI and altered activity/connectivity of neural networks, and to determine whether or not this is related to emotion regulation deficits.
- To identify EEG patterns in the acute and subacute phase after mTBI related to clinical parameters (loss of consciousness, post-traumatic amnesia, CT-scan abnormalities) as well as the above mentioned biochemical parameters and outcome.

Study design

A prospective multicentre cohort study in two level-1 trauma centres in the Netherlands (i.e. University Medical Centre Groningen, and Medisch spectrum Twente, Enschede).
During a two year period, patients with mTBI that are presented at the ED of the aforementioned hospitals, will be included and all data will be collected. Measurements will take place at the following four time points post-injury:

- Timepoint 1 (T1) at the ED.
- T2: at 2 weeks post-injury.
- T3: at 4-6 weeks post-injury.
- T4: at 6 months post-injury.

At T1, data regarding injury- and patient-related characteristics will be collected. Computed tomography (CT) scans will be performed according to the Dutch mTBI guidelines. Acute (baseline) post-traumatic complaints will be assessed by the physician at the ED. When they are full conscious and oriented, patients receive the study information and informed consent will be obtained. Time for consideration is 3 days. Because it is standard procedure to draw blood samples in the emergency setting, two extra blood samples (i.e. 7,5 mL per sample) will already be collected to minimize the burden. In case informed consent is not provided, these blood samples will be destroyed. Saliva samples will be collected immediately after informed consent, and 8 and 16 hours later . In case of persistent disorientation and amnesia, patients are admitted at the Neurology ward, and will be given the study information when their mental state recovers. For saliva collection, spouses or (an)other direct relative(s)

will be asked for premature consent. Material will of course be destroyed when patients are not willing to participate when they are asked for formal consent. At discharge, an information sheet is provided containing global information regarding the general course of recovery after TBI (which is standard procedure). The EEG study will take place at either the ED or the neurology ward, depending on whether the patient is admitted to the hospital. EEG will be performed within 24 hours after injury. Separate informed consent will be obtained. For patients that are still disoriented and/or have post-traumatic amnesia, deferred consent will be applied, and official written informed consent will be obtained when patients are compos mentis. In case the first emergency contact/partner/family is present, the EEG study will first be discussed with that person/them. In addition to healthy controls, we chose to include an orthopaedic control group at the ED, which allows us to control for a stressful and potentially inflammatory condition without brain injury.
Within two weeks, questionnaires will be send via email or regular mail to patients, to inquire whether there are residual complaints at T2, and to measure additional factors, such as anxiety and depression, coping style, personality characteristics, and emotion regulation skills. At T2, patients are also contacted by phone, and asked if they are willing to participate in the additional MRI- and/or hair cortisol studies. It has also been shown that an evaluation at 2 weeks post-injury is clinically beneficial for patients, as it offers the possibility to give extra education and reassurance, and if necessary, arrange referrals to specialists (e.g. neurologist, psychologist, rehabilitation specialist).
At T3, the follow-up, and additional measurements take place.
At T4, questionnaires will be send by email or via regular mail to determine outcome and measure persistent complaints. Patients will be reminded once by phone in case they do not return the questionnaires.

Study burden and risks

The measurements that are conducted in the study do not have any adverse consequences for the participants, and there are few if any risks for the participants. The burden of filling in questionnaires will be minimal (two time points; the first questionnaires taking approximately 30 minutes, the second 15 minutes). The first vena puncture is routinely performed for patients with mTBI, and will create no additional burden for this group. For orthopaedic controls this is not the case, and will create some additional burden. The second vena puncture (or the first and last for healthy controls) is short-lasting, but might also be stressing for certain participants. Electrocardiography (ECG) and saliva collection will create a minimal if any burden, and are therefore considered non-invasive. For subjects in the MRI-subgroups, participation is more intensive, as subjects in these groups have to undergo a 1 hour MRI-scan, and also having to perform an emotion regulation task during scanning. Hair-collection does not contain any burden, and based on our experience, does not cause any dramatic cosmetic changes. The EEG study will lead to limited additional burden. It will take approximately 20

minutes. Although there are no risks associated, it can cause some discomfort when placing the cap with the electrodes.
There are no additional benefits compared to standard care.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

Inclusion criteria are: patients with mild traumatic brain injury (mTBI) aged 18 years or older. Mild TBI is defined by a Glasgow Coma Scale score of 13-15 and/or loss of consciousness <= 30 minutes (Kayd et al. 1993). Inclusion criteria for the orthopedic control group are patients aged 18 years or older who sustained a minor injury to an extremity (e.g. sprain or uncomplicated fracture of wrist or ankle.

Exclusion criteria

Exclusion criteria for mTBI are: neurological or psychiatric co-morbidity, admission for prior TBI, drug or alcohol abuse, and mental retardation. For the orthopedic controls and healthy controls exclusion criteria are: neurological or psychiatric co-morbidity, previous TBI, drug or alcohol abuse, and mental retardation. Exclusion criteria for the MRI-study are implanted ferromagnetic devices or objects, pregnancy or claustrophobia. Language barriers or illiteracy, prohibiting understanding and completion of questionnaires are general exclusion criteria.

Study design

Design

Study type:	Observational invasive
Intervention model:	Other
Allocation:	Non-randomized controlled trial
Masking:	Open (masking not used)
Control:	Active
Primary purpose:	Basic science

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	17-01-2020
Enrollment:	700
Type:	Actual

Ethics review

Approved WMO

Date:	17-04-2019
Application type:	First submission
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)

Approved WMO

Date:	03-02-2021
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	04-01-2022
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	19-05-2022
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
CCMO	NL67252.042.18