Different courses of change in connectivity after mTBI depending on cognitive reserve and how this is related to symptoms and symptom resolution

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INTRODUCTION

The population-based rate of mild traumatic brain injury (mTBI) is estimated to exceed 600/100000 population per year in total, if including only patients seeking emergency care the estimated rate is approximately 100-300/100000 (1). Many patients recover within 3 months after injury but a sustainable proportion suffer from persisting symptoms, for instance fatigue, headaches, irritability (2).

Early identification of people at risk for long-term consequences after mTBI is important in order to arrange appropriate follow-up and treatment but due to the heterogeneity and non-specificity of the symptoms after mTBI this is not a simple task (3). A large prospective study found that 44 % of the patients showed incomplete recovery 6 months after injury, also noting that previous mental health problems and lesser education were related to worse outcome, whilst CT abnormality was not (4).

As conventional neuroimaging techniques have failed to detect the subtle alterations that may be important for prognosis and long-term outcome after mTBI, studies using fMRI have shown some interesting results (5, 6). Resting-state fMRI (rs-fMRI) measures functional connectivity, which may be disrupted by the effects of mTBI, by investigating co-activation patterns between distinct brain regions, when an explicit task is not being performed. Several studies have shown signs of hyper connectivity after mTBI, but the results are inconclusive regarding if hyperconnectivity is related to better or worse outcome (3). It is suggested that other variables, for instance demographic and cognitive variables, also need to be incorporated with imaging biomarkers when investigating the relationship between fMRI biomarkers with outcome after mTBI (3).

A marker related to demographic status and cognition that have shown to be relevant for outcome in brain injury or pathology is cognitive reserve (7). Cognitive reserve is defined as an aspect of the brain's function or structure that impacts the relationship between injury/pathology and outcome (8). Higher cognitive reserve is related to better outcome in conditions ranging from Alzheimer, MS and mTBI (9-11). Cognitive reserve is inherently abstract and hence measured by proxy measures such as length of education or tests of intelligence (8).

AIM/OBJECTIVES

To investigate whether change in connectivity over time after mTBI, according to fMRI, varies depending on cognitive reserve compared to orthopedic controls and how this is related to symptoms and symptom resolution.

METHODS

STUDY SETTING

Patients were recruited from the emergency department at Danderyd Hospital between January 2015 and April 2016. Baseline and follow-up assessments, including MRI scans were conducted at Danderyd University Hospital.

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PATIENT CHARACTERISTICS

15 patients with mTBI and 15 controls with a minor orthopedic injury were recruited. The orthopedic controls were in the same age span and consisted of patients of with minor traumatic injuries to the hand, arm, foot or leg with no need of surgical intervention.

ELIGIBILITY CRITERIA

Eligible patients in the mTBI group were consecutive patients, between 18 and 40 years of age, presenting at the emergency department at Danderyd Hospital (Stockholm, Sweden) between January 2015 and April 2016 due to an mTBI to such an extent that CT was indicated. mTBI was defined by a Glasgow Coma Scale (GCS, (12)) score between 13-15 and one or more of the following symptoms: <30 minutes loss of consciousness, <24 hours post-traumatic amnesia and/or a transient neurological deficit according to the WHO Collaborating center of Neurotrauma Task Force (13). Exclusion criteria were uncertain duration of loss of consciousness, if they had contraindications to MRI, if they had a previously acquired brain injury, a progressive neurological disorder or another injury/illness with short expected survival, if they were dependent of help in daily living before the current damage, if they had severe visual impairment or were non-Swedish speaking.

The orthopedic controls (OC; n = 15) were in the same age span and consisted of patients of with minor traumatic injuries to the hand, arm, foot or leg with no need of surgical intervention. These patients were non-systematically and intermittently included in the study during the same time frame as the mTBI patients. A prior history, within 2 years of the study, of a traumatic head injury in a need of medical attention was an exclusion criterion for controls.

OUTCOME VARIABLES

Table 1: Outcome measures

Outcome measure	Measures
Primary outcome measures	
State fatigability	Difference between score during the first 60 and the last 60 seconds of the Digit Symbol Substitution Test/Coding (DSST, (14)). The lower the score, the stronger the indication of fatigability
Self-rated post-concussion symptoms	For assessment of self-rated symptoms The Rivermead Post-Concussion Symptoms Questionnaire (RPQ, (15)) was used. RPQ is based on a Likert scale and includes 16 items with ratings from 0 to 4. Higher score indicates more symptoms.
Secondary outcome measures	
Trait fatigability	The Fatigue Severity Scale (FSS (16)) was used to measure trait fatigue. FSS consists of 9 questions and is based on a 7 point Likert scale A high score implies a higher level of fatigue.

Anxiety and depression	Hospital Anxiety and Depression (HADS, (17)) scale was used to screen for depression and anxiety, higher scores indicate more severe problems
Self-rated visual symptoms in near work	Convergence Insufficiency Symptom Survey (CISS, (18)) was used to assess near work-related visual symptoms. Total score is 60 and a value above 21 indicates a high level of symptoms.
Visual disturbances	A visual examination performed by a licensed optometrist, using standard optometric clinical methods. Diagnosis of visual dysfunction were based on established diagnostic criteria (19).

Sample Size

In order to detect differences in activation on a voxel level with alpha set to 0.05, 12 participants per group are needed to achieve 80 % power (20). 15 participants per group were recruited to compensate for expected attrition. The groups are matched regarding age, educational level and premorbid IQ.

Recruitment and analysis of non-participants

Patients were recruited at the emergency department at Danderyd Hospital. Consecutive patients, seeking care for mTBI or a minor orthopedic injury were asked to participate in the study.

Subject recruitment was conducted between January 2015 and January 2016 and was stopped when a total of 15 patients with mTBI and 15 orthopedic controls were enrolled, in accordance with the power calculation.

Among the 129 patients who were asked for participation in the study (32 mTBI; 97 OC), a total of 99 people declined, 17 mTBI and 82 OC. Of those who declined, 88% of mTBI and 64% of orthopedic subjects were men, and there was no difference regarding age between participating and non-participating individuals. The reasons stated for not participating were lack of time and inconvenience. Two individuals in the mTBI group and two individuals in the orthopedic control group were lost to follow-up despite several follow-up phone calls and letters.

Data Collection and Management

A prospective controlled, observational fMRI-study, with assessments on average 7 days after injury (span 2-12 days) and 122 days after injury (span 81-324 days).

Study patients were contacted by phone 1–3 days after injury. All study participants received written information about the study and gave informed consent. All data related to the injury, GCS on arrival at the emergency department and results of CT of the brain were collected from the medical records. Demographic data were collected by interview at the baseline examination. All study participants were scheduled to be assessed two times: at baseline, in the subacute phase (for patients with trauma, 7–10 days after the trauma) and at follow-up 75–100 days after the injury. Due to recruitment difficulties and in order to minimize drop-out, the time frame for the first and second assessments was extended. The median time between injury and baseline visual assessment was 7 days (range 4–13 days) for patients with mTBI and was 8 days (range 7–12 days) for orthopedic controls. The median time between injury and follow-up visual assessment was 103 days (range 81–232 days)

for patients with mTBI and 109 days (range 87–322) for orthopedic controls. No statistically significant difference was found between patients with mTBI and the orthopedic control group regarding time between the injury and assessments (baseline and follow-up). Patients with mTBI and orthopedic controls underwent examination with structural MRI and resting state functional MRI of the brain at baseline and at follow-up.

MRI Data Acquisition Protocol.

The MRI data acquisition was conducted on a whole-body 3T clinical MRI scanner (Philips Ingenia, Philips Healthcare, Best, Netherlands) equipped with a 20-channel phased-array receiving head coil. All data was acquired at Danderyd University Hospital, Stockholm, Sweden. The MRI data acquisition protocol included the following scanning sessions: (1) 3-plane localizer; (2) Conventional clinical MRI scans including 3D T1-weighted TFE, 2D FLAIR, T2-weighted FFE, T2-weighted TSE and DWI with 32 direction; (3) resting-state fMRI FE-EPI 8 min. The main acquisition parameters included the following: TE/TR 35/3000 ms, flip angle= 90°, 32 slices of 4 mm thickness, FOV= 230mm, matrix size= 96 × 96, data acquisition acceleration with SENSE parallel imaging method (acceleration 1.8), and 160 dynamic timeframes. Each participant's head was carefully fixed in in the head coil to reduce involuntary head motions. During the resting-state fMRI scans the participants were instructed to focus their sight on a white cross onto a black background projected on a screen installed in front of them. The participants were also instructed to not think about anything specific during the resting-state fMRI scans.

Resting-state fMRI data processing.

The resting-state fMRI datasets will be preprocessed using FSL (http://www.fmrib.ox.ac.uk/fsl) The first 5 timeframes in each data set will be removed to ensure signal steady state. Motion correction will be performed and the average volume for each motion-corrected time series will be used to generate a brain mask to minimize the inclusion of the extra-cerebral tissues. Spatial normalization to the standard MNI template will be performed using a 12-parameter affine transformation and mutual-information cost function. During the affine transformation the imaging data will also be re-sampled to isotropic resolution using a Gaussian kernel with 4mm full width at half maximum (FWHM). ICA analysis will be performed using the AFNI tool MELODIC and multi-session temporal concatenation. Individual estimates of the group level spatial maps will be calculated using the tool Dual Regression. Finally randomize permutation testing will be performed in order to look at group differences.

Measures

Self-assessment

For assessment of self-rated symptoms The Rivermead PostConcussion Symptoms Questionnaire (RPQ, (15)) was used. RPQ is based on a Likert scale and includes 16 items with ratings from 0 to 4. A score of 1 means that the symptom has been present but is no longer a problem and a score between 2 and 4 indicates symptom severity from 'mild to severe.'

Self-rated trait fatigability were rated with the Fatigue Severity Scale (FSS, (16)). FSS consists of 9 questions and is based on a 7 point Likert scale A high score implies a higher level of fatigue. It is one of the most frequently

used inventories for measuring fatigue in people with chronic illnesses and is considered to have robust psychometric properties (20).

Occurrence of depression and anxiety were screened with Hospital Anxiety and Depression Scale (HADS, (17)). The scale comprises of two separate scales for anxiety and depression. Scores range from 0 to 21, with scores from 0 to 7 representing a “normal,” 8–10 a “mild,” 11–14 a “moderate,” and 15–21 a “severe” level of anxiety or depression. The HADS has been widely used to assess anxiety and depression following TBI (21).

Self-rated near work related visual symptoms were measured with Convergence Insufficiency Symptom Survey (CISS, (18)). The CISS is a validated and reliable instrument which assesses both direct symptoms (eg. blurred vision, double vision) and indirect symptoms (eg. difficulty maintaining concentration, headache)(18). The survey includes 15 questions with ratings from 0 ”never” to 4 ”always”. Total score is 60 and the cut-off score for abnormally high levels of symptoms is 21.

Visual disturbances were measured by a licensed optometrist, using standard optometric methods. Included in the assessment was tests of visual acuity, refractive error, stereoacuity, accomodation, heterophoria, eye motility and fusional vergence. Diagnosis of visual dysfunctions were based on established diagnostic criteria (19).

Diagnosis of visual dysfunction was based on established diagnostic criteria. Visual functions were measured by a licensed optometrist, including assessment of refractive error, visual acuity, stereoacuity, heterophoria, fusional vergence, eye motility, near point of accommodation, and near point of convergence. A questionnaire, Convergence Insufficiency Symptom Survey (CISS), assessed visual strain during near work. Only convergence, accommodation, fusional vergence, and CISS will be analyzed in this project based on previous findings from the same dataset (22) and clinical experience.

NEUROPSYCHOLOGICAL ASSESSMENT

The Digit Symbol Substitution Test/Coding (DSST, (14)) from the Wechsler scales, is primarily used for measuring psychomotor processing speed. The task is ongoing for 120 s during which the participant is expected to fill in symbols paired to digits. The score is the number of symbols correctly completed, higher score indicates better result. In this study DSST was used to measure Fatigability (DSST-f). DSST-f was calculated by subtracting the score for the first half of the test (60 first seconds) from the last part of the test (60 last seconds). A negative score implies a slower performance during the latter part of the test, which is indicative of fatigability(23). DSST-f has previously been demonstrated to be a sensitive measure for fatigability, but not depression, in patients with mTBI (24).

The Swedish Lexical Decision Test was used at to assess premorbid IQ. The Swedish Lexical Decision test measures the premorbid estimated full-scale intelligence quotient (IQ), based on that word knowledge and cognitive functioning generally are associated, and that this association are relatively unaffected by TBI (25). In this test, the subject must make a lexical decision by judging if target words are real or fictitious. The Swedish Lexical

Decision Test has been demonstrated to explain 48 % of the variance of full-scale IQ from the WAIS-R and 31 % of demographic variables alone (25). If used in combination with demographic variables the estimation of premorbid cognitive functioning is further improved (25).

Data Management

All data material are recorded with a participant ID and will be unidentifiable. Only Catharina Nygren-DeBoussard and Marika Möller have access to the list that link participant ID with names. De-identified data will be electronically stored on the server at Danderyd University Hospital and will be deleted 10 years after the project has ended. The final dataset will be available to researchers actively contributing to statistical analyses and publications. Data entry will be controlled by initial exploratory analyses, including range checks, in order to promote data quality.

Confidentiality

Information on participants will be handled by health care professionals adhering to Swedish Law ensuring confidentiality and data protection. Results and data will be presented at a group level in publications, rendering identification of individual patients impossible. All data will be stored in accordance with the General Data Protection Regulation (GDPR).

Statistical Analysis

Descriptive statistics will be used to depict demographics, injury characteristics, results on neuropsychological tests and psychological screening instruments. Multi-subject and multi-session analysis based on general linear model will be performed and assessed using statistical tools including regression analysis and 2-way ANOVA.

Plans for communicating important protocol amendments to relevant parties

Important protocol modifications will be reported to the Ethics committee in Sweden and amendments will be made to the trial registry (Clinicaltrials.gov).

Dissemination plans

Publications are planned for journals in the fields of neuropsychology, and rehabilitation. Results will further be spread at relevant conferences, national and international meetings, and expert forums. The results will be shared with user organizations and its members as well as relevant policy makers.

Ethics

Ethics approval was obtained from the Regional ethical review board in Stockholm, diary no: 2014/597-31/1. The study adhered to the tenets of the Declaration of Helsinki.

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