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Chapter 21

Long-Lasting Mental Fatigue After Traumatic Brain Injury – A Major Problem Most Often Neglected Diagnostic Criteria, Assessment, Relation to Emotional and Cognitive Problems, Cellular Background, and Aspects on Treatment

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Additional information is available at the end of the chapter

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1. Introduction

Fatigue after traumatic brain injury (TBI) is common, but often overlooked. But for people fighting their fatigue after brain injury day after day, fatigue is a major problem. This post-injury mental fatigue is characterized by limited energy reserves to accomplish ordinary daily activities. Persons who have not experienced this extreme exhaustion which may appear suddenly, and without previous warning during mental activity, do not understand the problem. This is especially difficult to understand as the fatigue may appear even after seemingly trivial mental activities which, for uninjured persons, are regarded as relaxing and pleasant, as reading a book or having a conversation with friends. A normal, well-functioning, brain performs mental activities simultaneously throughout the day, but after a brain injury, it takes greater energy levels to deal with cognitive and emotional situations.

In this chapter, we highlight mental fatigue after TBI. In the case of long-lasting mental fatigue, it could be the only factor that keeps people from returning to the full range of activities that they pursued prior to their injury with work, studies and social activities. We describe mental fatigue and suggest diagnostic criteria and we also give a theoretical explanation for this. At the end of the chapter, we discuss treatment strategies and give some examples of possible therapeutic alternatives which may alleviate the mental fatigue.

Normally, the brain works in an energy-efficient manner and prominent energy reserves are present. This is due to well-functioning ion channel and amino acid transport systems and other effective physiological processes. After brain injury, some of these systems are down-regulated, and when mental energy requirements are high the physiological processes do not function to their full capacity; these cease to function efficiently with a resultant energy loss. This may be an explanation as to why the mental fatigue appears.

1.1. When does mental fatigue occur?

Annually, about 100-300/100 000 individuals sustain a TBI, and most of the injuries are mild in severity [1]. A majority of patients recover within one to three months following mild TBI [2, 3].

Fatigue is one of the most important long-lasting symptoms following TBI, and is most severe immediately after head injury. However it is difficult to arrive at any clear figure as to how common fatigue or, in particular, mental fatigue is. The reason for this is that different results have been obtained, and these are attributable to differences in definitions and differences in the methodology in the various studies. In follow-up studies, the frequency of prolonged fatigue varies from 16 up to 73 % [4-6]. There is no correlation between persistent fatigue and severity of the primary injury, age of the person at injury or time since injury [7, 8]. For those suffering from fatigue 3 months after the accident the fatigue remained relatively stable during longer periods [9]. In particular, for those subjects who were suffering from the syndrome one year after the accident improvement in the fatigue was limited [10].

In the above reports, fatigue is discussed in terms of a single construct, i.e. not differentiated between the physical or mental aspects. In this chapter, we consider mental fatigue as a separate construct and we discuss its relationship to cognitive and emotional symptoms.

1.2. Mental fatigue is not a separate diagnostic entity

Mental fatigue is not an illness, rather it represents a mental sequel, probably due to a disturbance of higher brain functions, either physical or psychological in origin. It is included in, and defined within the diagnoses Mild cognitive impairment (F06.7), Neurasthenia (F48.0) and Posttraumatic brain syndrome (F07.2) [11].

1.3. Typical characteristics of mental fatigue

A typical characteristic of pathological mental fatigue after TBI is that the mental exhaustion becomes pronounced during sensory stimulation or when cognitive tasks are performed for extended periods without breaks. There is a drain of mental energy upon mental activity in situations in which there is an invasion of the senses with an overload of impressions, and in noisy and hectic environments. The person feels that their brain is overloaded after a tiny load. Another typical feature is a disproportionally long recovery time needed to restore the mental energy levels after being mentally exhausted. The mental fatigue is also dependent on the total activity level as well as the nature of the demands

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of daily activities. Fatigue often fluctuates during the day depending on the activities carried out. Thus, this fatigue is a dynamic process with variations in the mental energy level. The fatigue can appear very rapidly and, when it does, it is not possible for the affected person to continue the ongoing activity. Common associated symptoms include: impaired memory and concentration capacity, slowness of thinking, irritability, tearfulness, sound and light sensitivity, sensitivity to stress, sleep problems, lack of initiative and headache [12].

For many persons, this mental fatigue is the dominating factor which limits the person's ability to lead a normal life with work and social activities. For most people, fatigue subsides after a period of time while, for others, this pathological fatigue persists for several months or years even after the brain injury has healed. Interestingly, however is that as many as 30% of family or friends interpreted fatigue as laziness [9].

Theories as to the mechanisms accounting for mental fatigue including our own theory, suggest that cognitive activities require more resources and are more energy-demanding after brain injury than usual [13, 14]. Thus, more extensive neural circuits are used in TBI victims compared to controls during a given mental activity [15]. This indicates an increased cerebral effort after brain injury.

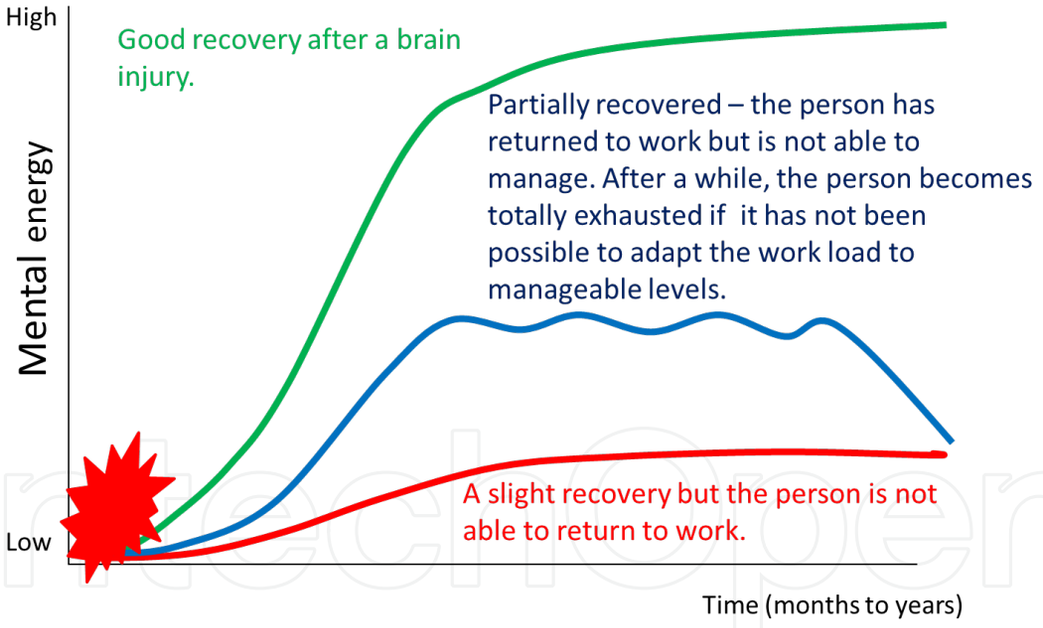

Figure 1. Schematic representation of recovery of mental energy after TBI. The green line represents a full recovery while the blue and red lines represent impaired recovery in terms of the mental energy levels. Persons whose recovery follows the blue line recover partially. On their return to work and daily activities, they are not able to manage and they become exhausted. Persons whose recovery follows the red line do not recover and are not able to return to work and daily activities.

Therapist Luann Jacobs describes mild TBI and the lack of energy and lack of endurance that many can experience. As they are able to do what is normal and what appears normal, they run the risk that their symptoms will be misunderstood [16].

"Mild brain injury is a real misnomer, as it conveys the idea that nothing much is a problem when quite the opposite is more often true. It is called "mild" because, in fact, the mildly brain injured can walk, talk, eat and dress independently, often times drive a car, shop, cook, go to school, or even work.

What the term fails to account for is the inherent limits of how often, for how long (endurance), and the all-important, how consistently (e.g., every day, once a week) these activities can be performed. Even more elusive is the concept of how many of these daily activities can be done sequentially in a given day as is normal in the lives of people who are not brain injured.

The fatigue they feel defies description, going far beyond and far deeper than anything a non-brain-injured person would consider profound exhaustion."

2. Theoretical explanation of mental fatigue

The cause of this extreme fatigue is not known. However, there are speculations that the symptom may be caused by dysfunction of the astrocytes, the most common supporting cells in the brain [17, 18]. As a consequence, nerve cell communications do not function properly.

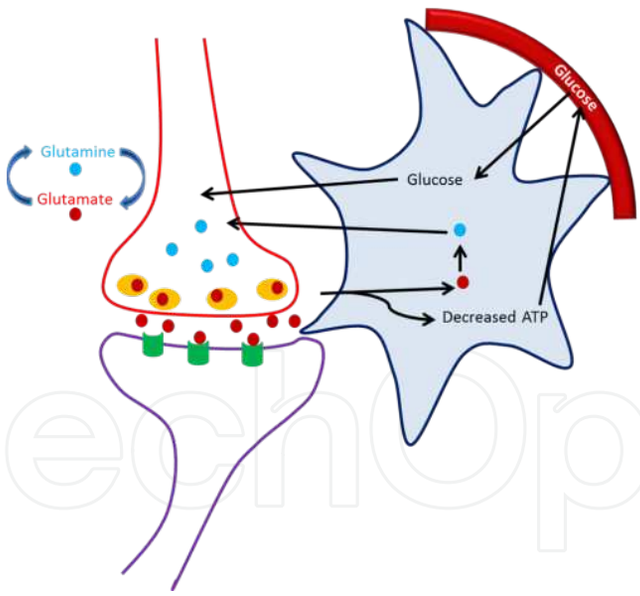

Figure 2. Schematic drawing of a synapse with glutamate as the transmitter and an astrocyte with processes surrounding the synaptic terminal. After being released from the presynaptic terminal (pre-syn; this is shown in red in the figure), glutamate interacts with glutamate recognizing receptors on the postsynaptic membrane (post-syn; shown in green in the figure). After stimulation of the postsynaptic neuron, glutamate is taken up by glutamate transporting systems on the astrocyte processes. Glutamate is converted to glutamine in the astrocyte and transported back to the presynaptic terminal where glutamine is converted back to glutamate. During this process, and with decreasing ATP levels as the signal, glucose is taken up from the blood to supply neurons and astrocytes with energy.

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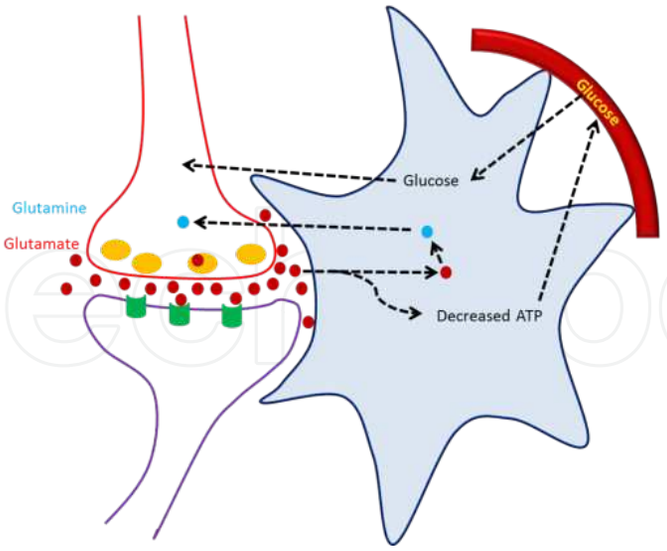

Figure 3. Following TBI there is a neuroinflammation with down-regulation of astroglial glutamate transport systems. If this state is not restored completely, there will be an impaired extracellular glutamate clearing with slightly increased extracellular glutamate levels, slight astrocyte swelling and impaired glucose uptake. Neuronal activity, if long-lasting, may result in energy crisis.

2.1. On cellular mechanisms probably underlying mental fatigue

Following TBI there is a low-grade neuroinflammation with down-regulation of astrocyte glutamate transporters and Na+/K+ ATPase activity [19, 20]. If these physiological systems are not restored completely there will be a dysfunctional support of the glutamate transmission. Glutamate signaling is essential for information processing, including learning and memory formation. Low levels and fine-tuning of extracellular glutamate are necessary to maintain high precision in information processing, and thereby high efficiency in the information handling within the CNS. Our hypothesis implies that such dysfunction could underlie the mental fatigue at the cellular level. From experimental data, the astroglial cells are considered the most important cells for clearing the extracellular space from glutamate during glutamate transmission. In addition, it is well-accepted from the experimental data that this clearing capacity is attenuated by substances or conditions associated with brain dysfunction or pathology (see [17]).

If the capacities of these processes are not fully restored, neuronal function is impaired in at least two ways: 1) extracellular glutamate levels increase upon neuronal activity leading to unspecific signaling and 2) lack of energy. In the event of a high mental load with high neuronal activity, these factors may lead to a metabolic collapse of neuronal circuits – we have previously called this a "dead-lock" situation, which may take a long time to restore.

We consider this metabolic failure as one probable explanation for the prominent and abrupt exhaustion that the TBI victims with mental fatigue can experience. The long restoring time at

a cellular level corresponds to the long time it takes for the TBI victims to restore mental activity.

One way to restore this dysfunction is to stimulate Na^+/K^+-ATPase along the dopaminergic circuits which regulate attention and executive functions. Possible candidates are methylphenidate and the dopaminergic stabilizer OSU6162 (see below under the heading, 'Treatment').

3. Assessment of mental fatigue

There is an abundance of scales for assessing fatigue in general and several of these scales are designed for use in different diseases [21, 22]. The scales include questions relating to feelings of fatigue, perceived impact on activities, affective feelings and mental or cognitive effects. Many of the scales are self-reported on a Likert or an ordered scale, with the following response alternatives: Never, Sometimes, Regularly, Often or Always.

We have developed and used the Mental Fatigue Scale (MFS) during the last five years. We decided to construct this scale since we were not able to find an assessment scale adapted to mental fatigue. The MFS is a multidimensional questionnaire containing 15 questions. It incorporates affective, cognitive and sensory symptoms, duration of sleep and daytime variation in symptom severity. The questions concern the following: fatigue in general, lack of initiative, mental fatigue, mental recovery, concentration difficulties, memory problems, slowness of thinking, sensitivity to stress, increased tendency to become emotional, irritability, sensitivity to light and noise, decreased or increased sleep as well as 24-hour symptom variations. The questions in the scale are based on common activities and we have related the estimation to exemplified alternatives. It is also possible to provide estimations in-between two alternatives. The intention was to make the scale more consistent between individuals and also between ratings for the same individual. The exemplified alternatives can help the person to respond in a similar way despite the present state of fatigue or emotional state. The MFS is designed in a similar way as The Comprehensive Psychopathological Rating Scale (CPRS). The CPRS also includes exemplified alternatives and it is used to record changes in psychopathology over a comparatively short period [23]. The questions included in the MFS are based on symptoms described following longitudinal studies of patients with TBI, brain tumours, infections or inflammations in the nervous system, vascular brain diseases, and other brain disorders, which indicates that an acquired brain injury or disorder can result in similar symptoms [24-26]. The scale is free to use and can be downloaded at www.mf.gu.se (both in Swedish and English). We have transcribed one of the questions in the MFS, below:

Mental fatigue

Does your brain become fatigued quickly when you have to think hard? Do you become mentally fatigued from things such as reading, watching TV or taking part in a conversation with several people? Do you have to take breaks or change to another activity?

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0	I can manage in the same way as usual. My ability for sustained mental effort is not reduced.
0.5	
1	I become fatigued quickly but am still able to make the same mental effort as before.
1.5	
2	I become fatigued quickly and have to take a break or do something else more often than before.
2.5	
3	I become fatigued so quickly that I can do nothing or have to abandon everything after a short period (approx. five minutes).

Figure 4 shows how healthy controls and subjects suffering from mild TBI, TBI and stroke have rated separate questions on the MFS. The brain injury victims were divided into different groups according to their total rating on MFS. When a person rates low on one question, the total rating on most of the separate questions will also be low, while persons rating high on one question on the MFS, will also rate most of the questions on a high level.

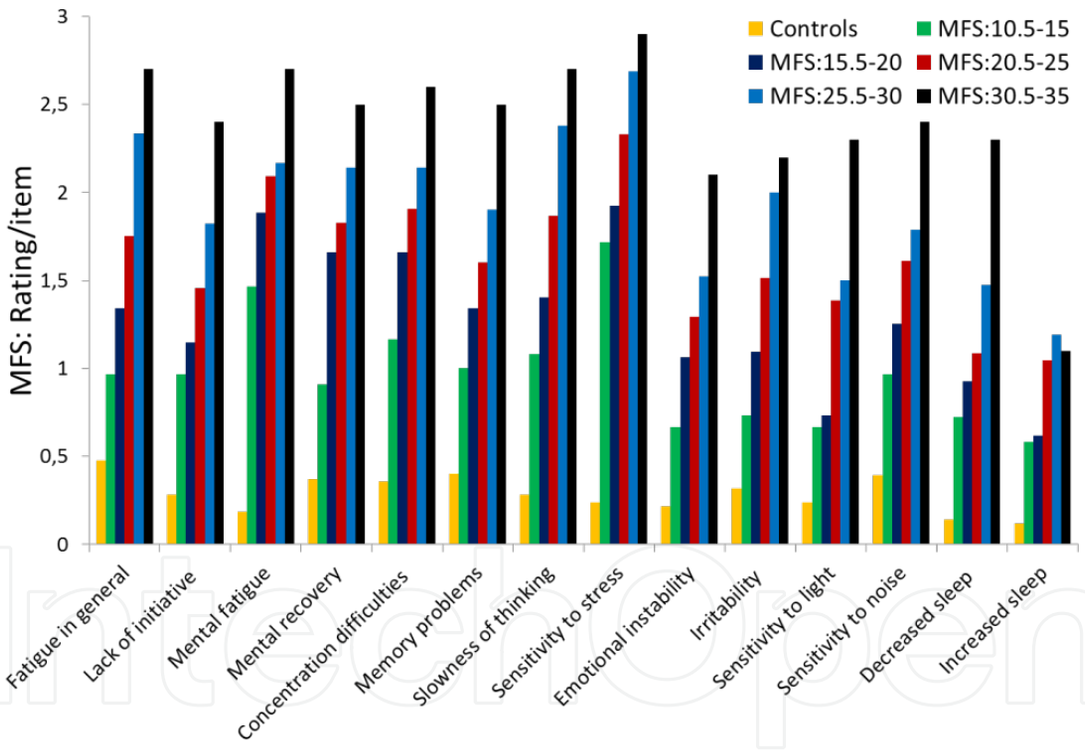

Figure 4. Rating on separate items on the Mental Fatigue Scale for controls and brain injured subjects. Brain injured subjects are divided into groups according to their total rating on MFS.

3.1. The use of MFS and results from the studies

The rating on MFS by healthy controls and people who suffered mild TBI or TBI did not reveal any significant differences between females and males, and there was no correlation between the results on MFS and age or education of the TBI victims (figure 5). Furthermore, we did not

find any correlation for the TBI participants concerning time since injury and their rating on MFS. We have, in our studies worked with participants with mental fatigue lasting for six months or periods greater than six months. At this stage, we do not have any data relating to ratings early after TBI or mild TBI. This accounts for the fact that the rating may lack correlation to time since injury.

The control group rated MFS significantly lower than mild TBI and TBI victims. The participants included for the analysis were healthy controls and participants who had suffered mild TBI or TBI without major depression. The participants were between 20-67 years of age.

We recommend a cutoff score on the MFS at 10.5. A score of 10.5 on the MFS was found to deviate significantly from the control sample and is also above the 99th percentile for the control group. A score above 10.5 implies a problem for the person, although a serious problem is not always the case. However, such a score implies the need for the person to consider the current situation with their work and/or social life. The MFS had a high internal consistency and all separate items were rated significantly higher among brain injured subjects compared with healthy controls (see also figure 5).

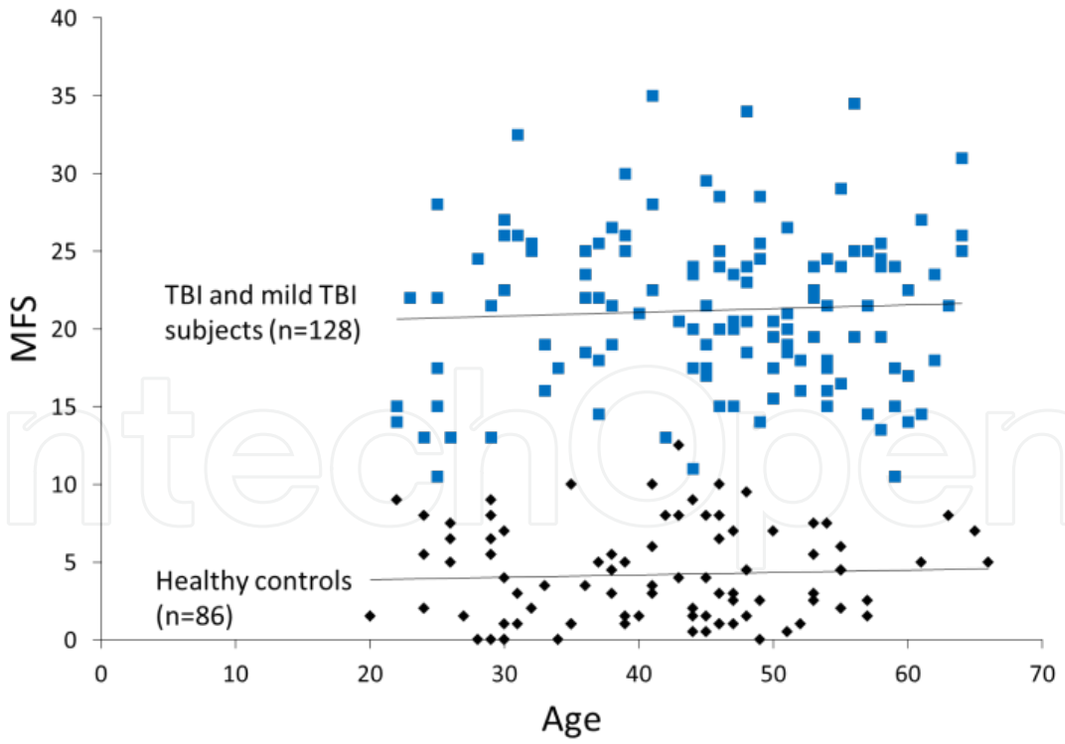

Figure 5. Correlation with age and rating on MFS for healthy controls and subjects with long-lasting mental fatigue after brain injury.

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4. Mental fatigue and connection to cognitive functions

It has been proposed that subjective mental fatigue after TBI or mild TBI correlates to poor performance in attention tests and reduced processing speed [13, 27, 29-34]. We also found that information processing speed, attention and working memory were significantly reduced for the brain injury victims (both mild TBI and TBI) compared to controls. Furthermore, the tests correlated significantly to the results on the MFS (figure 6). Among the cognitive functions, processing speed was found to be a significant predictor for the rating on MFS [27].

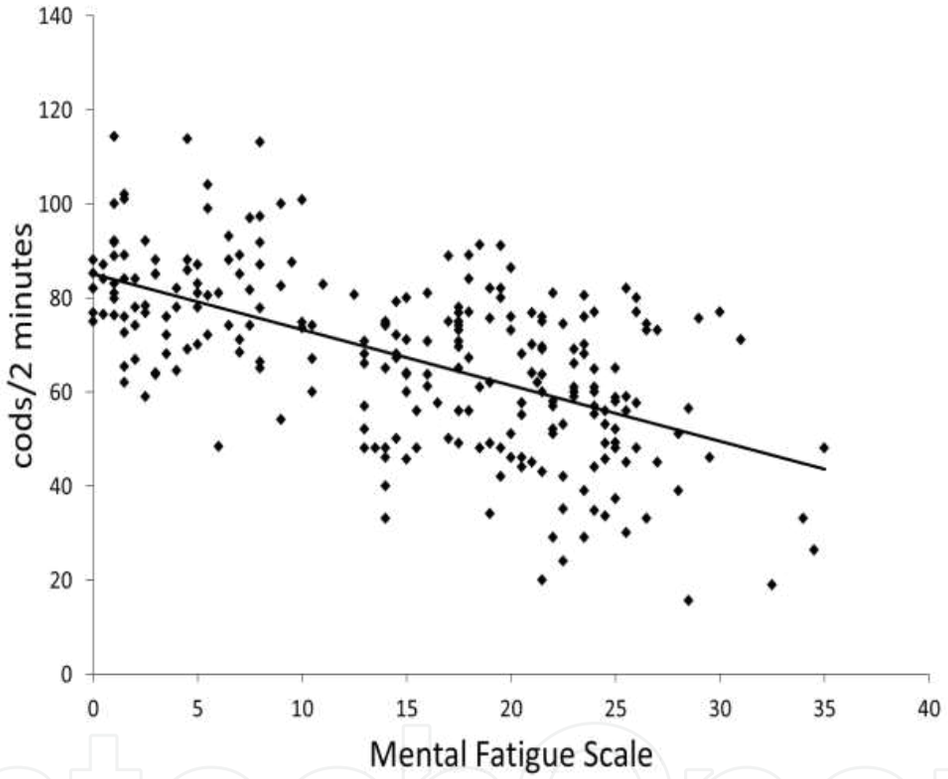

Figure 6. Correlation between Mental Fatigue Scale and information processing speed (Digit Symbol-Coding).

5. Mental fatigue and connection to emotional functions

In the population of TBI victims, depression is elevated although there is a wide variation in frequency, depending on methodological differences [35-37]. In our studies, we have included participants who complained of mental fatigue after TBI and we excluded subjects affected by major depression, as it was our intention to explore the mental fatigue component. Despite

this, we found, with the use of the CPRS/MADRS, that there was an elevation in the rating of depression items for TBI subjects compared to controls. The CPRS scale includes both a depression and an anxiety scale [23, 38]. The CPRS depression scale is also called the Montgomery-Åsberg Depression Rating Scale (MADRS) [39].

However, there are overlapping items in the MFS and CPRS. The overlapping items include the following: lack of initiative, concentration difficulties, irritability and decreased sleep. With a factor analysis, the items were separated into a mental fatigue component and a depression and anxiety component. Irritability was placed in the depression-anxiety component and the other three items in the mental fatigue component. With an analysis using the new components, we found that by adjusting the mental fatigue component this removed the difference observed between the brain injured subjects and controls in the depression-anxiety component. However, by removing the depression-anxiety component this did not have an effect on the difference observed between the brain injured subjects and controls in the mental fatigue component.

In this subject sample, we were able to demonstrate that a significant effect on the difference observed between the brain injured subjects and controls in the scores for depression can result in an overestimation if the effect of the mental fatigue component is not taken into consideration. This indicates that mental fatigue and depression must be treated as separate constructs and it is also important to make this distinction for the purposes of therapeutic strategies.

6. Definition and diagnostic criteria for long-lasting mental fatigue

The diagnostic criteria for posttraumatic brain syndrome include most of the symptoms that are often present along with mental fatigue. However, we suggest mental fatigue to be a central symptom after a brain injury reflecting an inefficient support to the neuronal networks.

Mental fatigue is a lack of mental energy with impaired cognitive, emotional and sensory functioning. Mental fatigue is characterized by an unusual feeling of fatigue or malaise. There is a drain on the person's mental energy upon mental activity. The result is a diminished attention and concentration capacity. Situations which involve high levels of external cues and an overload of impressions are strenuous. Failing energy levels and excessively long recovery times are the result of over-exertion. The condition impairs the person's ability to function in their work, studies and gatherings with family and friends.

6.1. How to recognize long-lasting mental fatigue

- The mental fatigue has persisted for at least 1 month;
- The sum of scores from the MFS is 10.5 points or above.

Typical symptoms include:

- An unusually rapid drain of mental energy upon mental activity;

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- Impaired attention and concentration capacity over time;
- Following over-exertion, a long recovery time disproportionate to the exertion level;
- Diurnal variation of the fatigue symptom with the fatigue often being better in the mornings and worse in the afternoons and evenings; variations from one day to the next;
- Usually one or several associated symptoms (see below):

The following additional or associated symptoms are common:

- Mood swings, irritability and stress intolerance;
- Trouble with memory;
- Sleep problems;
- Sensitivity to, or intolerance of light and loud noise;
- Headaches following over-exertion.

Sleep problems most often occur in the following way: either a shorter duration of sleep with interrupted wake-ups or sleeping more than usual. If the person becomes more mentally fatigued, the sleep will most often become worse, and if the person rests for some days the sleep can become improved again. The emotional load may increase the severity of the fatigue, but if mental fatigue exists, it will remain even once the emotional components, as depression or anxiety have been treated. However, it is important to treat the emotional problems. In this way, the mental fatigue may, to some extent be relieved.

6.2. If the fatigue is not acknowledged in time, this may result in the following

- A total and almost paralyzing fatigue;
- Longer periods of rest may be needed, often over several days;
- A worsening of symptoms over time;

6.3. Mental fatigue symptoms are often present in the following situations

- Situations in which there is an invasion of the senses with an overload of impressions, and noisy and hectic environments such as crowded events, also the hustle and bustle of shopping centers, and travelling by bus, etc.;
- Reading books and newspapers;
- Conversations with people – this becomes more of a struggle when more people are involved;
- Unexpected events.

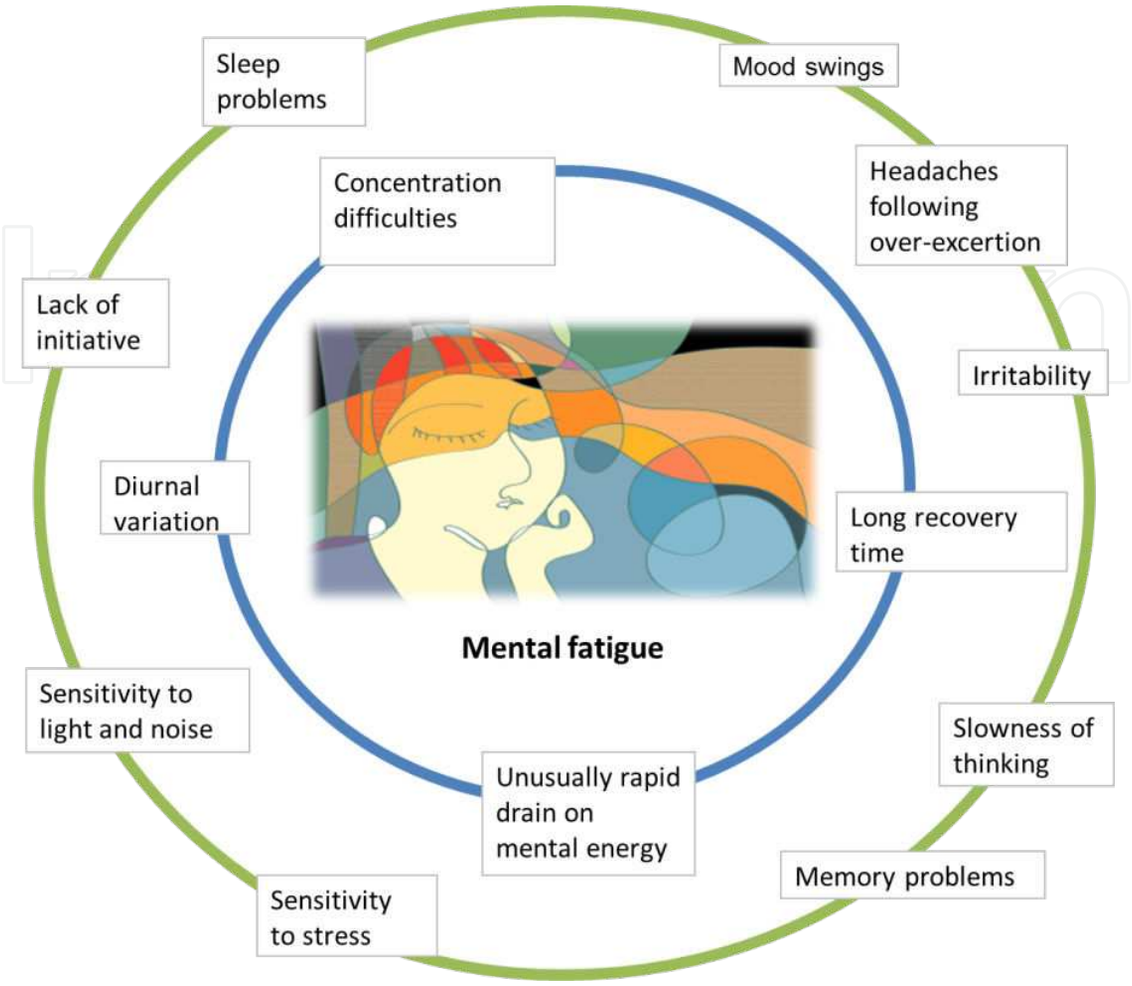

Figure 7. The figure illustrates mental fatigue. Characteristic symptoms are seen on the blue circle and associated symptoms on the green circle. (The figure in the middle is illustrated by Kristina Edgren Nyborg).

7. Treatment

There is currently no effective treatment for mental fatigue. For many people, there is an increased risk of doing too much and becoming even more fatigued. Today, the most important recommendations are to adapt to the energy available by doing one thing at a time, resting regularly and not overdoing things.

When mental fatigue is present, it is important to adapt work as well as daily activities to levels that the brain can manage. However, this is challenging for most people and it may take a long time, even years, to adapt to a sustainable level. It may also be difficult for the person to learn by himself/herself and it can take several years of considerable struggle, frustration, despair and depression, to find the right balance between rest and activity. Professional support is required but this can be hard or impossible to find especially when mental fatigue continues for many years.

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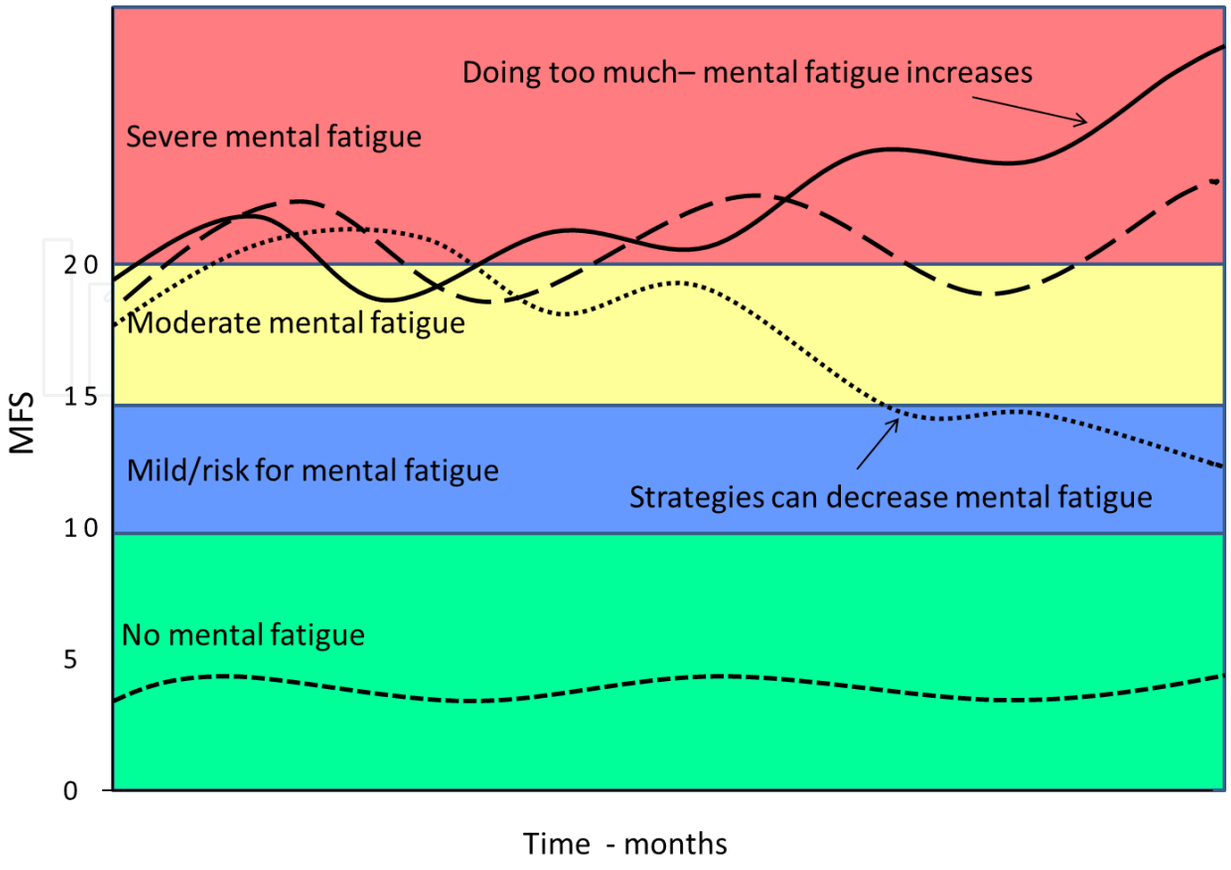

Figure 8. The figure illustrates levels and fluctuations in mental fatigue measured with the MFS after TBI and variations over time. Most mild TBI victims recover completely (green field) and do not exceed 10 points on the MFS. People within the blue, yellow or red fields suffer from metal fatigue to varying extents. It is also shown that treatment strategies decrease the mental fatigue, while over-exertion leads to increased rates on the MFS.

7.1. Treatment strategies

- Take regular breaks;
- Encourage rest before becoming over-tired;
- Try to work at a steady pace, taking one task at a time with short working periods, and prioritize the tasks;
- Plan the days' activities or the activities for the week in a diary or journal. Avoid over-exertion.

The use of strategies is important. By resting the brain as much as possible the mental energy will be alleviated. However, the brain and the individual also need positive experiences and stimulation to ensure wellbeing. It is difficult to achieve this balance between rest and stimulation.

7.2. Treatment studies for alleviating mental fatigue

When mental fatigue becomes a prolonged problem, it is essential to be able to alleviate the symptoms. We have reported on significantly reduced mental fatigue after treatment using the mindfulness-based stress reduction (MBSR) program [40, 41]. We have also reported on possible therapeutic strategies to reduce mental fatigue by means of pharmacological treatments, using neurostimulant substances as methylphenidate [42] which affects dopamine and norepinephrine signaling. We have also reported on a new substance not currently available on the market, (-)-OSU6162, which is a dopamine and serotonin stabilizer [43].

7.2.1. Mindfulness

The MBSR program was tested on TBI and stroke victims suffering from long-term mental fatigue [40]. MBSR is a clinically-effective

method for a wide range of conditions as stress, depression, pain, and fatigue after cancer, with the potential to help individuals to cope with their difficulties [44-47]. MBSR is also suggested to be linked to improvements in attention and cognitive flexibility [48] and also to changes in brain neuronal connectivity [49].

MBSR includes a range of both formal and informal practices. The intervention is based on Kabat Zinn's MBSR program [50]. The formal practices in MBSR are described by M. Cullen 2011 [51] and these include gentle Hatha yoga with an emphasis on mindful awareness of the body, a body scan designed to systematically, region by region, cultivate an awareness of the body without the tensing and relaxing of muscle groups associated with progressive relaxation, and sitting meditation with an awareness of the breath as well as a systematic widening of the field of awareness to include all four foundations of mindfulness: awareness of the body, feeling tone, mental states and mental contents. As such, the intention of MBSR is much greater than simple stress reduction. The program consists of eight weekly group sessions which are each approximately 2.5 hours long, one day-long silent-led retreat between sessions six and seven and home practice of about 45 minutes, six days a week. The participants receive guided instructions and CDs for home practice.

We found a significantly reduced mental fatigue after the MBSR program and participants improved their processing speed significantly compared to control on waitlist [40]. Improvement was independent of gender, time since injury and age. Another recent study with MBSR for mild TBI patients showed a similar result with significant improvement in quality of life, perceived self-efficacy, working memory and attention [52]. Furthermore, a small-scale study of 10 mild TBI subjects included in the MBSR program over a 12-week period also showed a significantly improved quality of life and decreased depression rating [53]. The effects were maintained one year later among the seven contactable participants. They also noted an improvement in reported energy levels at the follow-up [54]. However, after TBI, a short MBSR program over a 4-week period did not result in any cognitive or emotional changes [55].

The results demonstrate that mindfulness practice may be a therapeutic method well-suited to subjects suffering from mental fatigue after brain injury. One reason why MBSR was effective may be that this treatment offers strategies to better handle stressful situations

appropriately and economize with mental energy. Despite the problem of ensuring that participants stay awake, which is one of the fundamental aspects of meditation, it was possible to adjust mindfulness to suit the needs of mental fatigue subjects and to improve their wakefulness as well as reducing their mental fatigue levels.

7.2.2. Methylphenidate

Methylphenidate inhibits dopamine and noradrenalin reuptake resulting in increased extracellular concentration of dopamine and noradrenalin [56]. Methylphenidate has been used for many years in the treatment of ADHD in children, in the first instance to increase wakefulness, attention and concentration capacity. Methylphenidate has also been tested on TBI victims with positive effects on information processing speed and, to some extent on working memory and attention [57-63]. Guidelines for use of methylphenidate for deficits of attention and processing speed after TBI have been suggested [64], while no such guidelines exist for fatigue following TBI.

In an open randomized study, methylphenidate significantly improved mental fatigue dose-dependently as assessed with the MFS [42]. The item, pain was also studied and we found that this item was rated high by most of the subjects in our study as the participants were recruited on the basis of the items, TBI and pain. However, no significant alleviation of pain was reported as a result of methylphenidate treatment. However, it is important to note that pain can hide posttraumatic brain injury symptoms or mental fatigue which is not always connected to the actual pain. We also found that there was no interaction between the pain and the mental fatigue in those participants treated with methylphenidate. These findings indicate that, not only is it necessary to treat patients for the pain for which they are primarily referred to the clinic, but also for the mental fatigue, if present.

Methylphenidate was well-tolerated by TBI subjects. However, tolerance of methylphenidate differed between subjects and we therefore recommend starting treatment with an initial low dose.

7.2.3. (-)-OSU6162

The monoaminergic stabilizer OSU6162 interacts with both dopaminergic and serotonergic systems. It appears to act as an antagonist on a binding site of the D2 receptor. More recent research has demonstrated that OSU6162 also exerts a stabilizing effect on serotonergic neuronal circuits, acting as a partial 5-HT2A agonist [65, 66].

In two randomized, double-blind and placebo-controlled studies we found statistically significant alleviation of mental fatigue after a stroke or TBI by OSU6162 during 4 weeks' treatment with active drug [43]. However, the numbers of patients in these studies were small (21 TBI and 19 stroke victims). Further studies are needed, with a larger number of patients and, in particular longer treatment periods as mental fatigue may be long-lasting. Adverse reactions were mild and could be avoided by dose adjustment. Several patients experiencing such adverse reactions expressed the wish to receive continued treatment with the drug.

Similar results were detected for methylphenidate and OSU6162. These drugs were shown to have the effect of both alleviating mental fatigue and increasing information processing speed.

8. Conclusions

Mental fatigue can become a prolonged and distressing problem after TBI having considerable effect on life and wellbeing. It is important to acknowledge and assess mental fatigue when discussing the options regarding therapeutic methods as the mental fatigue has been the result of a TBI.

After TBI, mental energy levels are failing, and the brain needs to rest. It is not possible to improve the mental energy with training in order to perform more mental activities. In fact, training with a view to resting the brain is what is important. Suitably-adapted and energy-saving strategies are important and most patients need support in order to achieve an enduring balance between activities and rest as this is difficult, it takes a long time and may be frustrating.

The treatment studies we reported on are aimed at helping the person to manage their life better. However, it is important to stress that there is a risk that the medication can compel the person to do more than is appropriate. The reason for this is that, most often they want to carry out activities in a similar way as before the injury and have been longing for the chance to be able to do this. The problem is that, for most persons suffering from long-term mental fatigue after TBI, the activity levels are close to the threshold of what they are able to sustain. This makes them susceptible if they increase their activity levels too much. With mindfulness most participants reported on more energy, but they also became more pleased and happy with life. Mindfulness also gave them a tool to use and they could take command over their own lives; how it is here and now, not longing for a better life or ruminating over what has been. This also saves energy! A combination with neurostimulants and mindfulness may be a good therapeutic strategy.

In the future, research is warranted for early treatment with the intention to reduce the development of long-term mental fatigue. We also need to better elucidate and carry out an in-depth analysis of mental fatigue.

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