

Long-Lasting Mental Fatigue After Recovery from Meningitis or Encephalitis – A Disabling Disorder Hypothetically Related to Dysfunction in the Supporting Systems of the Brain

Lars Rönnbäck and Birgitta Johansson
*Institute of Neuroscience and Physiology,
Sahlgrenska Academy, University of Gothenburg
and Sahlgrenska University Hospital,
Gothenburg,
Sweden*

1. Introduction

Fatigue may originate from peripheral or central causes, thus being “physical” or “cognitive” (mental) in nature. Some authors also put forward the concepts “primary” or “secondary” fatigue (DeLuca, 2005). It may be that the different dimensions of fatigue have different neurobiological and neurophysiological correlates (see also Chaudhuri and Behan, 2000; 2004). The big problem, however, is that in-depth analyses of different types of fatigue have yet to be performed.

In this paper we focus on cognitive, or mental, fatigue (Johansson & Rönnbäck, 2012; Rönnbäck & Hansson, 2004), which in some cases can be long-lasting after meningitis or encephalitis. According to the International Classification of Diseases, 10th revision (ICD-10), the cognitive symptoms are covered by the diagnoses “mild cognitive disorder” or “neurasthenia” and according to the *Diagnostic and Statistical Manual of Mental Disorders*, 4th edition (DSM-IV) (American Psychiatric Association, 1994) they are included in the group of “mild neurocognitive disorders”. According to the diagnostic classification by Lindqvist and Malmgren (1993), the symptoms belong to the “astheno-emotional syndrome”.

The fatigue that we describe is characterized by a pronounced fatigability that may appear even after moderate mental activity. Characteristically the recovery time after being exhausted is long. We discuss diagnostics and we extend our previously proposed cellular mechanisms underlying this mental fatigue in brain disorders (Rönnbäck & Hansson, 2004) and suggest that functions of the supporting systems, namely the glial cells, in the brain are out of balance. Thus, dysfunction in the blood-brain barrier (BBB) permeability (see Abbott et al, 2006) due to inflammatory activity with microglial activation and the production of cytokines might be responsible for an attenuated astroglial fine-tuning and support of the neuronal glutamate signalling, which is of utmost importance for information processing in the brain.

2. Symptoms associated with the mental fatigue

A number of symptoms often appear in relation to the mental fatigue. These are noise- and light sensitivity, irritability, affect-lability, stress-intolerance and headache (table 1).

- DECREASED CONCENTRATION CAPACITY
- SUBJECTIVE MEMORY DISTURBANCE
- NOISE SENSITIVITY
- LIGHT SENSITIVITY
- AFFECT LABILITY
- IRRITABILITY
- STRESS SENSITIVITY
- SLEEP DISTURBANCE
- HEAD ACHE

Table 1. Symptoms often accompanying the mental fatigue in CNS infections/inflammations or brain disorders.

3. Mental fatigue and depression

Fatigue and depression are important topics, to some degree overlapping as fatigue is on one hand a dominant symptom of and on the other hand, has been considered a risk factor for depression (Johnson et al., 1996). There is evidence supporting the idea that states of fatigue present variations of depression, while other studies argue for a more pure fatigue state, with little overlap with depression. Many studies on brain injury report increased susceptibility to depression after the injury, even if fatigue is also very common (Ashman et al., 2004; Silver et al., 2009; Whelan-Goodinson et al., 2009). Depression and mental fatigue can occur alone, but they sometimes occur simultaneously in states of CNS inflammation, infection or degeneration. The two states may overlap in symptomatology, but the core symptoms included in depression and mental fatigue, respectively, are different. Mental fatigue is mostly related to concentration and attention, especially over time, and is dependent on the degree of mental load. The fatigue fluctuates over the day, and the recovery period after mental exhaustion is mostly un-proportionally long. Persons suffering from depression, on the other hand, present low-spiritedness and a decreased interest in their surroundings. Many also find it difficult to feel pleasure. These persons may even experience fatigue but mostly throughout the day (see also Lerdal et al., 2011). The long-term mental problems after a well rehabilitated infection or inflammation in the CNS may relate to mental fatigue, as depression, if present, usually alleviates after some period while the mental fatigue persists.

Our hypothesis includes a tentative explanation on the basis of transmitter pathophysiology that persons suffering from long-lasting mental fatigue may be more vulnerable to depression (see below and figure 3).

4. On the diagnostics of mental fatigue

4.1 Assessment of mental fatigue: In clinical practice, fatigue is often noticed, but not always as important and central as it could be. This may be due to that it is subjective and

there are limited possibilities to assess it objectively. Therefore, the problems caused by mental fatigue have not until now generated any extensive research. Mental fatigue is treated by many professionals as an issue of secondary importance.

As mental fatigue has such a great impact on many functions, it is important to consider the problem from a wide perspective and to look at the issue with an open mind, in order to develop an understanding of the cause of the problem. Mental fatigue is something specific, but it is easy to misunderstand this symptom. It could be mistaken for apathy if the person has difficulties with getting things done during the day, is not interested in learning new things and is not doing things that interest him or her. However, these problems, instead, could be the result of low energy levels, as is typical for mental fatigue. In this state it might be too exhaustive to carry out activities that demand a high degree of concentration, as talking to friends, reading and learning new things.

4.1.1 Self-assessment of mental fatigue

Fatigue is usually assessed as a subjective problem with self-report questionnaires, and there are many self-assessment scales trying to catch different forms of fatigue in various states or diseases. As life-prolonging therapy exists for persons with HIV/AIDS, chronic fatigue is one disabling symptom among these persons. A 56-item self-report instrument was developed by Pence and co-workers (2008) to specifically describe HIV-related fatigue with the aim to measure the intensity and consequences of fatigue as well as the circumstances surrounding fatigue in people living with HIV.

We focused on the mental fatigue which we consider as the limitation for work and social activities in different infectious and inflammatory CNS diseases and we constructed a self-assessment scale partly adapted from Rödholm et al (2001). This self-reported questionnaire contains 15 questions which cover the most common symptoms occurring after brain injury (TBI) (King et al., 1995). The selection of items is based on many years of clinical experience and reports (Lindqvist & Malmgren, 1993). The questions include symptoms reported early on, as well as a long time after a brain injury or neurological diseases. The questions relate to 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 variations.

The items are based on common activities and the estimation relates to intensity, frequency and duration with exemplified alternatives. The intention was to make the scale more consistent between individuals and also between ratings for the same individual. Each item comprises examples of common activities to be related to four response alternatives. A higher score reflects more severe symptoms. A rating of 0 corresponds to normal function, 1 indicates a problem, 2 a pronounced symptom and 3 a maximal symptom. It is also possible to provide an answer which falls in between two scores (see example below).

Example of a question from the self-assessment scale of mental fatigue.

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?

- 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).

The self-assessment scale for mental fatigue and related items was evaluated. Significant correlations were found between all the 14 questions (24-hour variation was not included as only 'yes' and 'no' responses were measured). The 14 questions had adequate internal consistency. The Cronbach's alpha scale was used, giving a reliability coefficient of 0.944 (Johansson, et al., 2009). This indicates that the core problem with mental fatigue comprises a broader spectrum of relevant items with either primary or secondary symptoms. The response alternatives are refined in such a way as to make the self reports more consistent. This might have resulted in a more definite deviation from the healthy controls (the scale can be downloaded at www.mf.gu.se).

Many participants gave spontaneous comments on the scale as it includes important, key items which had previously been confusing for them. From a clinical viewpoint, the self-assessment scale can be a valuable therapeutic tool for the patient as it can clearly describe mental fatigue and common symptoms which co-occur. A better understanding of the problem is a very good starting point for further treatment (see also below). The self assessment scale may be valuable even for people with infectious or inflammatory CNS diseases and we hope that this scale will facilitate research on the prevalence, etiology and consequences of mental fatigue among persons suffering from diseases or disorders in the CNS.

4.1.2 Cognitive tests

With the intention of finding sensitive neuropsychological tests to assess mental fatigue, we chose tests measuring information processing speed (the time required to execute a cognitive task within a finite time period) (DeLuca & Kalmar, 2007), attention, working memory, verbal fluency and reading speed. The tests were digit symbol-coding from the WAIS-III NI (Wechsler, 2004), measuring information processing speed. Attention and working memory, both auditory and visual, were measured by means of the digit span and spatial span (Wechsler, 2004). Both tests included repetition of forward series of random numbers or blocks in order as well as in reverse. The verbal fluency test (FAS) measures the ability to generate as many words as possible beginning with a specific letter within one minute (Ellis et al., 2001). Parts A and B of the Trail Making Test (TMT), (Reitan & Wolfson, 1985) were used to measure visual scanning, divided attention and motor speed (Lezak et al., 2004). The test consists of a series of connect-the-circle tasks. The tasks in part A is to connect the circles in a sequence with a numerical order of 1 to 25. Part B comprise letters and digits in alternating numerical and alphabetical order, which have to be completed as quickly as possible. In order to evaluate higher demands such as dual tasks, a series of new

tests was constructed with three and four factors, respectively. The same number of circles (25) was used in all parts. The alternation between factors was similar to part B but months was added in part C and both months and days of the week in chronological order in part D. In the latter, the order of letters and digits was changed. The reading speed was measured using the DLS reading speed test used for the screening of dyslexia (Madison, 2003).

After TBI information processing speed and attention tasks were found to be most sensitive and were significantly decreased compared to healthy control, while no such effect was found for both visual and auditory working memory. The subjective rating of mental fatigue and related symptoms was primarily linked to processing speed and attention and processing speed was found to be the primary predictor for mental fatigue. The total sum of scores also correlated significantly with percentages for sick leave (Johansson, et al., 2009). Information processing speed is also the cognitive function most likely to be affected after a brain injury (Frencham et al., 2005; Madigan et al., 2000; Martin et al., 2000).

The self-assessment scale in combination with tests that primarily measure information processing speed and a high cognitive load on attention might make it possible to evaluate problems described by patients with mental fatigue, as subjective mental fatigue at least after mild TBI and TBI are suggested to primarily correlate with objectively measured information processing speed. If cognitive decline within these neuropsychological regions are evident, the mental loading can be even higher.

We now turn to the cellular level to visualise what happens during a mental process. We focus on the glutamate signalling under normal conditions and in disorders, preferentially infections or inflammations within the CNS, when the astroglial support is attenuated.

5. Astroglial support of neuronal glutamate signaling (figures 1 and 2)

It is estimated that the human brain consists of 10^{11} neurons and 3-5 times as many glial cells. One single neuron may have contacts with many thousand other neurons. Thus it is easy to understand that the human brain has the prerequisites for extensive communication with both the surrounding milieu and with other neurons within the brain. Glutamate is the most frequent excitatory transmitter, which is also involved in mental activities including learning and memory formation. When the transmitter has fulfilled its functions at the post-synaptic neuron, it must be removed to allow new impulse traffic. The astrocytes, the prominent supporting cell type in the CNS, regulate the extracellular glutamate levels ($[Glu]_{ec}$) and are thus responsible for clearing the extracellular space from excessive glutamate. It is generally considered that the $[Glu]_{ec}$ has to be maintained at approximately 1-3 μM in order to avoid excitotoxic actions of glutamate on neurons (Choi, 1992), and also to assure a high signal-to-noise ratio (high precision) in normal glutamate neurotransmission (Yudkoff et al., 1993). The astrocytes express high-affinity Na^+ -dependent electrogenic transporters: the glutamate aspartate transporter (GLAST) and glutamate transporter 1 (GLT-1) which are most abundantly located on astrocyte processes surrounding synapses of glutamatergic neurons (Danbolt, 2001). GLT-1 is today considered as the most important transporter for removal and regulation of $[Glu]_{ec}$ at synaptic transmission. GLT-1 is expressed on astrocytes only in the presence of glutamatergic neurons (Björklund et al., 2010), and the amount and efficiency increase when there is a high neuronal activity (Perego et al., 2000) (figure 1).

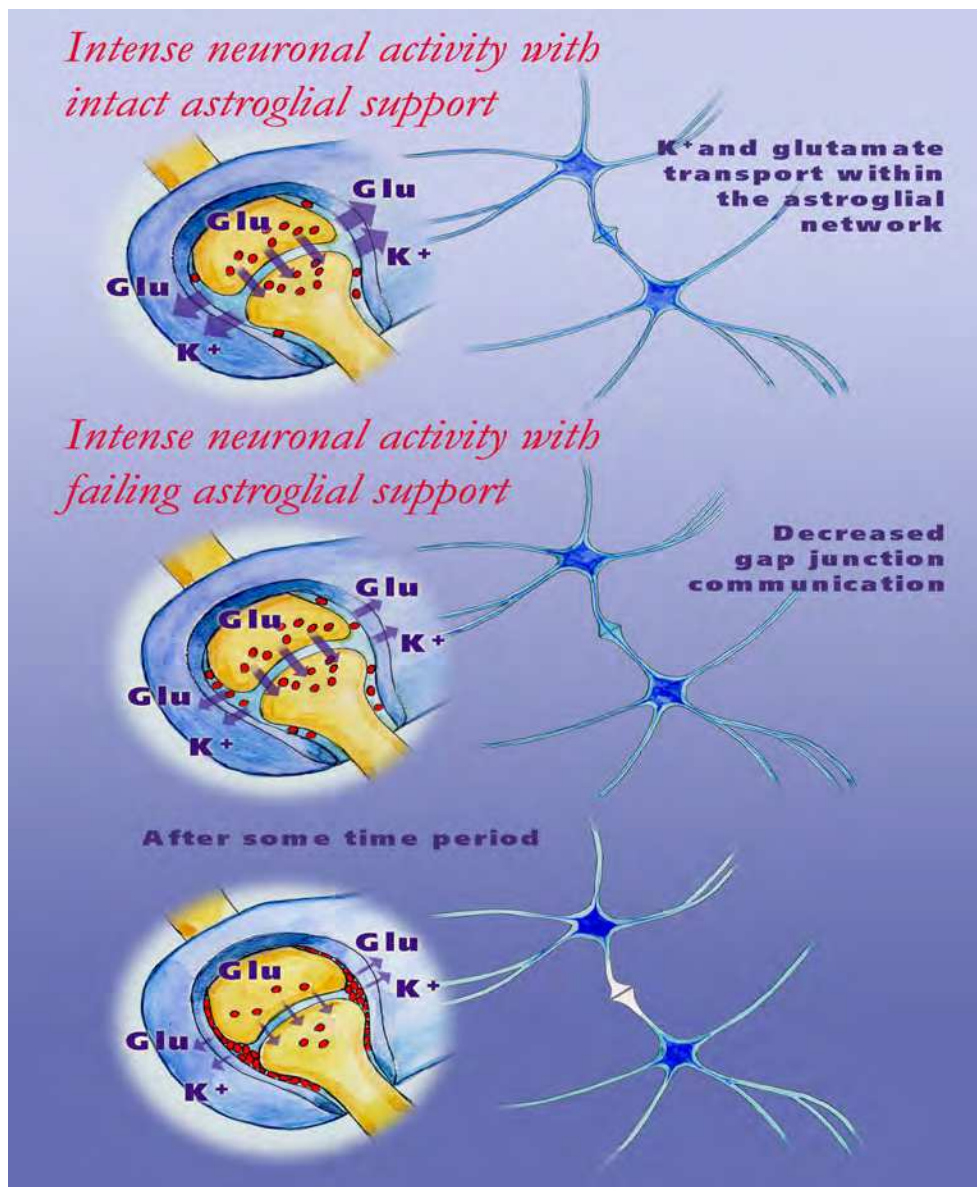


Fig. 1. Glutamate is released from the presynaptic terminal and affects postsynaptic glutamate receptors (left; upper figure). Thereafter glutamate is rapidly removed from the synaptic region by surrounding astroglial cells. A diminished astroglial glutamate uptake capacity leads to a decreased precision (signal-to-noise ratio) in the glutamatergic transmission (left; middle and lower figure). Astroglial networks that support neuronal glutamate signaling are shown to the right in the figures. (modified from Hansson & Rönnbäck, 2004 and drawn by Eva Kraft, Gothenburg, Sweden)

Let us make a simplified description of the situation around a neuron that is active in a mental process. This neuron is connected to other neurons in a network and signals are propagated from and to other neurons (figure 2). The propagation depends on the state of a number of synapses on the cell body and on the processes so that the neuron is polarized in a suitable way.

A great number of synapses could be activated in this process. Astroglial processes reach every synapse, and the astroglial cells regulate glutamate and ion levels in the synaptic cleft to set the proper sensitivity for an action potential (Hansson & Rönnbäck, 1995; 2003; Hertz & Zielke, 2004). When the astroglial cells take up glutamate their cell volume will increase somewhat, primarily due to osmosis, and normally this limited swelling is restored when the glutamate is transformed within the astroglial cell. If we perform intense mental activity, the neuron is reactivated frequently and the restoration done by the astrocytes will be delayed. In this situation the astrocytes can recruit help from other, nearby situated, astrocytes. The number of adjacent, activated neurons may also increase prominently. This may limit the support that can be provided from nearby astrocytes. If there is an intense neuronal activity for a longer period of time, the astroglial support can reach a state of saturation in which the transport capacity of extracellular substances is limited due to e.g. decreased extracellular space. As a consequence the neuronal polarization level will be continuously high, action potentials will be spontaneously triggered, and the mental precision will probably decrease - we experience fatigue. After a short break, however, we are mentally ready for new activities, or ready to continue the previously performed mental work.

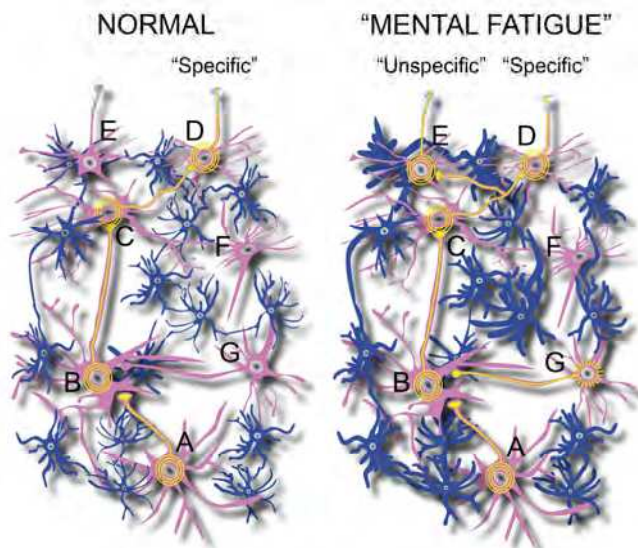


Fig. 2. Illustration of neuronal networks consisting of the nerve cells A-G (red) under physiological conditions (left figure). Cell A activates (yellow) B synaptically whereafter C, and later D is activated. Surrounding astroglial cells (blue) recognize the neuronal activity and interact with the neurons. The result will be that the “specific” response is carried forwards.

After a brain injury or other brain disorder (right figure) there could be a sprouting, which results in the activation of both neurons D and E by neuron C. Through the mechanism of glutamate “spill-over”, and also due to the slightly increased level of extracellular glutamate, neuron G will be activated, which in turn lead to the activation of neuron B. The overall result will be activation of larger neuronal circuits, astroglial swelling, and “unspecific” signalling in addition to the “specific” one. Thus, the “noise” in the signaling is somewhat increased. The increased swelling of the glial cells further strengthens and reinforces these processes due to the decreased extracellular space.

6. Impaired astroglial glutamate uptake capacity in neuroinflammation

After brain injury the GLT-1 expression is down-regulated and the glutamate uptake impaired (Torp et al., 1995; Rao et al., 1998; Szymocha et al., 2000; Legay et al., 2003; Yi et al., 2004; Persson & Rönnbäck, 2012). The mechanisms underlying this down-regulation are not fully understood. The GLT-1 protein is sensitive for oxidative stress due to its content of cysteines that are sensitive to oxidative formation of cysteine bridges. Furthermore, GLT-1 is sensitive to the acidic milieu and the pro-inflammatory cytokines TNF-alpha and IL-1beta (for ref, see Rönnbäck & Hansson, 2004).

7. Cellular mechanisms underlying mental fatigue – a hypothesis (figure 3)

If the astroglial fine-tuning of $[Glu]_{ec}$ is impaired, there would be decreased precision in the glutamate signalling. This is, according to our hypothesis, the basic cellular disturbance underlying the impaired concentration and memory capacity, which we experience as cognitive or mental fatigue (see Rönnbäck & Hansson, 2004). As a consequence, the signals taken into the brain will be handled in a less distinct way, resulting in ambiguous information. Due to its indistinct character, more information will be recognized as “new” by sensory brain centers, and will therefore be allowed to travel to the cerebral cortex and be processed there. The overall result may be that more, and larger, neuronal circuits would be activated over time (figure 2). With impaired GLT-1 function, local $[Glu]_{ec}$ could increase.

In CNS infections or inflammations, meningitis or encephalitis, pro-inflammatory cytokines are produced due to microglial activation (Andersson et al., 2005), and as GLT-1 is sensitive to TNF-alpha and also IL-1beta, the astroglial glutamate uptake capacity is impaired. Locally increased $[Glu]_{ec}$ could give rise to astroglial swelling, whereby the extracellular space shrinks (Sykova, 2001). The result would be disturbed fine-tuning of the glutamate signaling, and impaired transport of substances in the extracellular space (volume transmission). Astroglial swelling would give rise to relative depolarization of the astroglial cell membrane, with a further decreased astroglial glutamate uptake capacity, and in addition, a decreased capacity of the astrocytes to remove $[K^+]_{ec}$. Even moderately increased (up to 8–10 mM) $[K^+]_{ec}$ levels have been shown in experimental systems to inhibit glutamate release (Meeks & Mennerick, 2004). It should be noted that in states of decreased astroglial glutamate uptake capacity, even astroglial glucose uptake, and consequently the supply of metabolic substrates to the neurons, has been reported to decrease (see Hertz & Zielke, 2004). In addition, glutamate release from the presynaptic terminals could decrease due to impaired glutamine supply of the neurons. The result will be metabolic exhaustion and thereby decreased transmission.

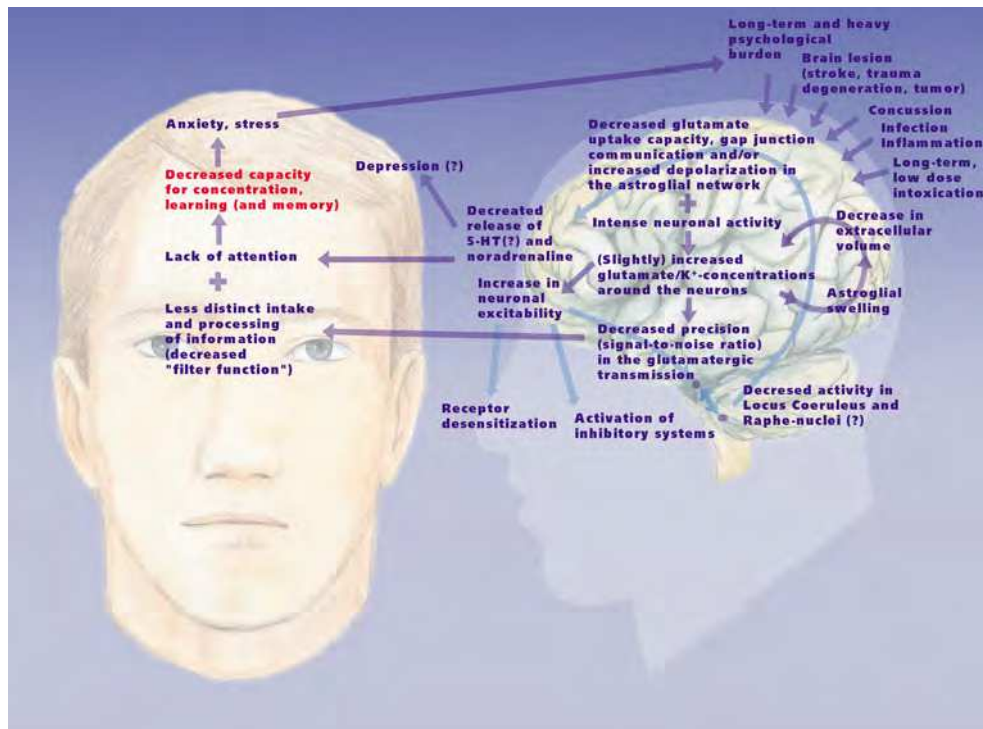


Fig. 3. A model for the development of mental fatigue due to brain disorder. Astroglial glutamate uptake capacity is impaired due to infection/inflammation, stroke or brain trauma (upper right in the figure). When there is an intense neuronal activity, this decreased capacity by the astroglial cells to clear extracellular glutamate levels could lead to impaired fine-tuning of glutamate and K⁺ levels around the neurons. The result might be impaired precision (signal-to-noise ratio) in the glutamatergic transmission. Astroglial swelling will further impair the regulation of neuroactive substances in the extracellular space due to decreased extracellular space volume. Furthermore, it is known from animal experiments that increased neuronal excitability in the frontal lobe impair the activities in the Locus Coeruleus and the Raphe nuclei (Sara & Hervé-Minvielle, 1995). If this is the case even in humans, we could have a neurobiological basis for decreased attention, which is commonly experienced by the patient, due to decreased dopamine, 5-HT and noradrenaline levels. The person (left in the figure) might experience information intake and processing to be less distinct and in combination with the impaired attention, experience mental fatigue upon mental activity. Secondary anxiety and stress could aggravate the symptoms by interaction with the glucocorticoid system, which is also known to interact with astroglial glutamate regulation (Zschocke et al. 2005; Persson & Rönnbäck, 2012; drawn by Eva Kraft, Gothenburg, Sweden)

Our hypothesis, presented schematically in figure 3, can thus explain why persons with these mental fatigue symptoms could perform cognitive tasks well for short periods, but in situations with increased sensory stimulation, they become completely exhausted, and it takes a long time for them to recover their cognitive capacity.

8. Support for our hypothesis

It is well accepted today that, in addition to meningitis or encephalitis, ischemia, TBI as well as degenerative disorders are associated to neuroinflammation with activation of microglial cells and the production of cytokines within the CNS (see e.g. Persson & Rönnbäck, 2012 for review). Even in states of no obvious neuronal damage, like major depression, lack of sleep, and so called sickness-behavior, where the mental fatigue could be very prominent, there is an inflammatory reaction in the brain with the production and release of cytokines (see e.g. Hashioka, 2011). From experimental systems it is also well-known that administration of interleukin (IL)-1 can result in decreased learning and memory capacity (Huang et al., 2010; Imamura et al., 2011). In this respect it is of utmost interest to note that in states with long-term pain, in which the permeability of the BBB is shown to be increased, inflammatory activity with the production and release of cytokines in the CNS is also demonstrated. From a clinical point of view it is well known that these patients often suffer from mental fatigue (see also Hansson & Rönnbäck, 2004; Nijs et al., 2012). Thus, inflammation within the CNS with activation of microglial cells and the production of inflammatory mediators may be one mechanism underlying the mental fatigue, in which one cellular mechanism may be an impaired astroglial glutamate regulation. It is a well-known fact that this regulation is sensitive to inflammatory mediators. Furthermore, Lange and co-workers (2005) demonstrated that difficulties in cognitive functions in persons suffering from Chronic Fatigue Syndrome are not only related to poor motivation, but indeed they provided evidence that these persons used increased neural resource allocation when they are processing more complex auditory information. This is also in line with our suggestions. A further support of biological origin for at least some portion of fatigue in persons with CNS inflammation, especially SLE, was reported by Harboe and co-workers (2008) who found fatigue associated with cerebral white matter hyperintensities.

9. Can mental fatigue be treated?

Pathologic mental fatigue can be induced by CNS infections, inflammations or irreparable neuronal injuries. This is the case in MS, stroke and TBI, as well as in degenerative disorders. In these states it is of utmost importance to start treatment early, before new neural inter-connections are established (see Dancause et al., 2005; Hansson & Rönnbäck, 2003). It is important to diminish the risk for secondary anxiety. After infections or mild TBI, the mental fatigue can be prominent even in the absence of significant neuronal injury. Early information about the often good prognosis of the disorder is therefore important. In addition, it is important for the person to learn about the symptoms and his/her own possibilities to limit the symptoms for instance by avoiding stress, and thereby avoid getting into mental exhaustion. Drugs which inhibit inflammation and cell swelling might be of value if our hypothesis turns out to be correct. Furthermore, inhibition of pro-inflammatory cytokines is probably of value in order to strengthen the glutamate uptake capacity by the astroglial cells. Such drugs do not exist in the market today and it is interesting to note that late results have shown that local glutamate levels dictates adenosine receptor regulation of neuroinflammation (Dai et al., 2010) suggesting the requirement of a fine-tuning of drugs being effective in the treatment of mental fatigue. However, promising results at least concerning the wakefulness were reported by Rabkin and co-workers (2011) using Armodafinil. We have tested a mindfulness-based stress reduction (MBSR) program on stroke or TBI victims with promising results (Johansson et al., in preparation). It has to be

investigated whether such therapy is valuable even for persons suffering from long-lasting mental fatigue after a meningitis or encephalitis.

10. Conclusion

Fatigue, especially mental fatigue, is common in states with infection or inflammation in the central nervous system (CNS) (Schmidt et al., 2006; Berg et al., 2010) as well as after a stroke (Choi-Kwon & Kim, 2011) or in degenerative diseases as Parkinson's disease (Friedman et al., 2011). For most persons the fatigue attenuates timely in parallel with the alleviation of the infection, but in a number of persons the mental fatigue may remain over months or years, even after recovery from the infection. Characteristic for this mental fatigue is that the person is able to be mentally active just for short periods, and a prominent fatigability may arise upon even moderate mental activity. Typically the recovery time, i.e. the time to get the mental energy back, is long. It may be difficult for the person to go back to work, as our high-technology society with its increasing demands on peoples' mental capacity does not accept anything but full engagement, even over time.

From a neurobiological point of view, the mental fatigue could be due to impairment of information processing capacity in the brain. Information processing is energy consuming and requires wide-spread and specific neural signaling. In states of brain dysfunction the information processing capacity is reduced.

In meningitis or encephalitis there is a neuro-inflammation with production of cytokines and other inflammatory compounds. It is well known that several of these substances impair the astroglial capacity to remove glutamate from the extracellular space. Glutamate signaling is essential for information processing in the brain, including learning and memory formation. Astroglial cells are responsible for the fine-tuning of extracellular glutamate which is considered necessary to keep a high efficiency in the information handling within the CNS.

We here extend our previously presented hypothesis on probable cellular mechanisms underlying mental fatigue after brain trauma and suggest that a remaining slightly impaired astroglial glutamate handling may at least partly explain long-lasting mental fatigue after recovery from a meningitis or encephalitis. The reason that the mental fatigue may be long-lasting in a number of such victims, but far from all, is not known (see Wait & Schoeman, 2010). Genetic or pre-morbid factors or states could be of importance (see also Lundin et al., 2006; Loeb et al., 2008).

11. Acknowledgements

The work performed in the authors' laboratory was supported by the Swedish Research Council and by LUA/ALF from the Sahlgrenska University Hospital and Edit Jacobson's Foundation.

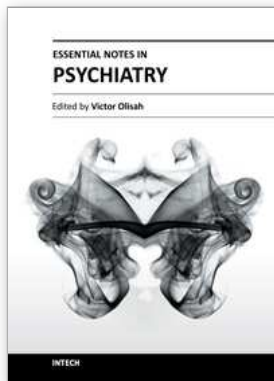
12. References

- Abbott, N.J., Rönnbäck, L. & Hansson, E. (2006). Astrocyte-endothelial interactions at the blood-brain barrier. *Nature Rev Neurosci*, 7,41-53.
- American Psychiatric Association, *Diagnostic and statistical manual of mental disorders*, 4th ed. Washington DC: American Psychiatric Association, 1994.

- Andersson, A.K., Rönnbäck, L. & Hansson, E. (2005). Lactate induces tumour necrosis factor- α , interleukin-6 and interleukin-1 β release in microglial- and astroglial-enriched primary cultures. *J Neurochem*, 93, 1327-1333.
- Ashman, T. A., Spielman, L. A., Hibbard, M. R., Silver, M. J., Chandna, T., & Gordon, W. A. (2004). Psychiatric challenges in the first 6 years after traumatic brain injury: Cross-sequential analyses of axis I disorder. *Arch Phys Med Rehabil*, 85(Suppl 2), S36-S42.
- Berg, P.J., Smallfield, S. & Svien, L. (2010). An investigation of depression and fatigue post West Nile virus infection. *S D Med*, 63, 127-129.
- Björklund, U., Persson, M., Rönnbäck, L. & Hansson, E. (2010). Primary cultures from cerebral cortex and hippocampus enriched in glutamatergic and GABAergic neurons. *Neurochem Res*, 35, 1733-1742.
- Chaudhuri, A. & Behan, P.O. (2000). Fatigue and basal ganglia. *J Neurol Sci*, 179, 34-42.
- Chaudhuri, A., & Behan, P. O. (2004). Fatigue in neurological disorders. *Lancet* 363, 978-988.
- Choi, D.W. (1992). Excitotoxic cell death. *J Neurobiol*, 23, 1261-1276.
- Choi-Kwon, S. & Kim, J.S. (2011). Poststroke fatigue: an emerging, critical issue in stroke medicine. *Int J Stroke*, 6, 328-336.
- Dai, S.S., Zhou, Y.G., Li, W., An, J.H., Yang, N., Chen, X.Y., Xiong, R.P., Liu, P., Zhao, Y., Shen, H.Y., Zhu, P.F. & Chen J.F. (2010) Local glutamate level dictates adenosine A2A receptor regulation of neuroinflammation and traumatic brain injury. *J Neurosci*, 30, 5802-5810.
- Danbolt, N.C. (2001). Glutamate uptake. *Prog Neurobiol*, 65, 1-105.
- Dancause, N., Barbay, S., Frost, S.B., Plautz, E.J., Chen, D., Zoubina, E.V., Stowe, A.M. & Nudo, R.J. (2005). Extensive cortical rewiring after brain injury. *J Neurosci*, 25:10167-10179.
- DeLuca, J. (ed.) (2005). *Fatigue as a Window to the Brain*. A Bradford Book, The MIT Press, Cambridge, Massachusetts, London, England, 336pp.
- DeLuca, J., & Kalmar, J. H. (Eds.). (2007). *Information processing speed: How fast, how slow, and how come? In: Information processing speed in clinical population*: Taylor and Francis group, New York.
- Ellis, D. C., Kaplan, E., & Kramer, J. H. (Eds.). (2001). *Delis-Kaplan Executive Function System – D-KEFS*. San Antonio, TX: The Psychological Corporation.
- Frencham, K. A. R., Fox, A. M., & Maybery, M. T. (2005). Neuropsychological studies of mild traumatic brain injury: a meta-analytical review of research since 1995. *J Clin Exp Neuropsychol*, 27(3), 334-351.
- Friedman, J.H., Abrantes, A. & Sweet, L.H. (2011). Fatigue in Parkinson's disease. *Expert Opin Pharmacother* 12, 1999-2007
- Hansson, E. & Rönnbäck, L. (1995). Astrocytes in glutamate neurotransmission. *FASEB J*, 9, 343-50.
- Hansson, E. & Rönnbäck, L. (2003). Glial neuronal signaling in the central nervous system. *FASEB J*, 17, 341-348.
- Hansson, E. & Rönnbäck, L. (2004). Altered neuronal-glia signaling in glutamatergic transmission as a unifying mechanism in chronic pain and mental fatigue. *Neurochem Res*, 29, 989-996.
- Harboe, E., Greve, O.J., Beyer, M., Goransson, L.G., Tjensvoll, A.B., Maroni, S. & Omdal, R. (2008). Fatigue is associated with cerebral white matter hyperintensities in patients with systemic lupus erythematosus. *J Neurol Neurosurg Psychiatry*, 79, 199-201.
- Hashioka, S. (2011). Antidepressants and neuroinflammation: can antidepressants calm glial rage down? *Mini Rev Med Chem*, 11, 555-564.
- Hertz, L. & Zielke, H.R. (2004). Astrocytic control of glutamatergic activity: astrocytes as stars of the show. *TRENDS in Neurosci*, 27, 735-43.

- Huang, Z.B. & Sheng, G.Q. (2010). Interleukin-1 β with learning and memory. *Neurosci Bull*, 26, 455-468.
- Imamura, Y., Wang, H., Matsumoto, N., Muroya, T., Shimazaki, J., Ogura, H. & Shimazu, T. (2011). Interleukin-1 β causes long-term potentiation deficiency in a mouse model of septic encephalopathy. *Neuroscience*, 187,63-69
- Johansson, B., Berglund, P., & Rönnbäck, L. (2009). Mental fatigue and impaired information processing after mild and moderate traumatic brain injury. *Brain Injury*, 23(13-14), 1027-1040.
- Johansson, B. & Rönnbäck, L. (2012). Mental fatigue; a common long term consequence after a brain injury. InTech, ISBN Brain Injury - Functional Aspects, Rehabilitation and Prevention (ISBN 979-953-307-025-3), Vienna, Austria.
- Johnson, S.K., DeLuca, J. & Natelson, B.H. (1996). Depression in fatiguing illness: comparing patients with chronic fatigue syndrome, multiple sclerosis and depression. *J Affect Disord*, 39, 21-30.
- King, N. S., Crawford, S., Wenden, F. J., Moss, N. E. G., & Wade, D. T. (1995). The Rivermead post concussion symptoms questionnaire: a measure of symptoms commonly experienced after head injury and its reliability. *J Neurol Neurosurg Psychiatr*, 24, 587-592.
- Lange, G., Steffener, J., Cook, D.B., Bly, B.M., Christodoulou, C., Liu, W.C., Deluca, J. & Natelson, B.H. (2005). Objective evidence of cognitive complaints in Chronic Fatigue Syndrome: a BOLD fMRI study of verbal working memory. *Neuroimage*, 26, 513-524.
- Legay, V., Deleage, C., Beaulieux, F., Giraudon, P., Aymard, M. & Lina, B. (2003). Impaired glutamate uptake and EAAT2 downregulation in an enterovirus chronically infected human glial cell line. *Eur J Neurosci*, 17,1820-1828.
- Lerdal, A., Gay, C.L., Aouizerat, B.E., Portillo, C.J. & Lee, K.A. (2011). Patterns of morning and evening fatigue among adults with HIV/AIDS. *J Clin Nurs*, 20, 2204-2216.
- Lezak, M. D., Howieson, D. B., & Loring, D. W. (Eds.). (2004). *Neuropsychological assessment* (4th ed.). New York:: Oxford University Press.
- Lindqvist, G., & Malmgren, H. (1993). Organic mental disorders as hypothetical pathogenetic processes. *Acta Psychiatr Scand*, 88(suppl 373), 5-17.
- Loeb, M., Hanna, S., Nicolle, L., Eyles, J., Elliott, S., Rathbone, M., Drebot, M., Neupane, B., Fearon, M., & Mahony, J. (2008). Prognosis after West Nile virus infection. *Ann Intern Med*, 149, 232-241.
- Lundin, A., de Boussard, C., Edman, G., & Borg, J. (2006). Symptoms and disability until 3 months after mild TBI. *Brain Injury* 20(8), 799-806.
- Madigan, N. K., DeLuca, J., Diamond, B. J., Tramontano, G., & Averill, A. (2000). Speed of information processing in traumatic brain injury: modality-specific factors. *J Head Trauma Rehabil* 15(3), 943-956.
- Madison, S. (2003). *Läsdiagnos*. Lund: Läs och skrivcentrum.
- Martin, T. A., Donders, J., & Thompson, E. (2000). Potential of and problems with new measures of psychometric intelligence after traumatic brain injury. *Rehabil Psychol*, 45(4), 402-408.
- Meeks, J.P. & Mennerick, S. (2004). Selective effects of potassium elevations on glutamate signaling and action potential conduction in hippocampus. *J Neurosci*, 24,197-206.
- Nijs, J., Meeus, M., Van Oosterwijck, J., Ickmans, K., Moorkens, G., Hans, G. & De Clerck, L.S. (2012). In the mind or in the brain? Scientific evidence for central sensitisation in chronic fatigue syndrome. *Eur J Clin Invest*, 42, 203-212.
- Pence, B.W., Barroso, J., Leserman, J., Harmon, J.L., & Salahuddin, N. (2008). Measuring fatigue in people living with HIV/AIDS: psychometric characteristics of the HIV-related fatigue scale. *AIDS Care*, 20, 829-837.

- Perego, C., Vanoni, C., Bossi, M., Massari, S., Basudev, H., Longhi, R. & Pietrini, G. (2000). The GLT-1 and GLAST glutamate transporters are expressed on morphologically distinct astrocytes and regulated by neuronal activity in primary hippocampal cocultures. *J Neurochem*, 75,1076-1084.
- Persson, M. & Rönnbäck, L. (2012). Microglial self-defence mediated through GLT-1 and glutathione. *Amino Acids*, 42, 207-219
- Rabkin, J.G., McElhiney, M.C. & Rabkin, R. (2011). Treatment of HIV-related fatigue with Armodafinil: a placebo-controlled randomized trial. *Psychosomatics*, 52, 328-336.
- Rao, V.L., Baskaya, M.K., Dogan, A., Rothstein, J.D. & Dempsey, R.J. (1998). Traumatic brain injury down-regulates glial glutamate transporter (GLT-1 and GLAST) proteins in rat brain. *J Neurochem*, 70,2020-2027.
- Reitan, R. M., & Wolfson, D. (Eds.). (1985). *The Halstead-Reitan neuropsychological Test Battery. Theory and clinical interpretation*. Tucson, AZ: Neuropsychology Press.
- Rödholm, M., Starmark, J.-E., Svensson, E., & von Essen, C. (2001). Asteno-emotional disorder after aneurysmal SAH: reliability, symptomatology and relation to outcome. *Acta Neurol Scand*, 103, 379-385.
- Rönnbäck, L. & Hansson, E. (2004). On the potential role of glutamate transport in mental fatigue. *J Neuroinflammation*, 1, 22.
- Sara, S.J. & Hervé-Minvielle, A. (1995). Inhibitory influence of frontal cortex on locus coeruleus neurons. *Proc Natl Acad Sci U S A*, 92, 6032-6036.
- Schmidt, H., Heimann, B., Djukic, M., Mazurek, C., Fels, C., Wallesch, C.W. & Nau, R. (2006). Neuropsychological sequelae of bacterial and viral meningitis. *Brain* 129, 333-345.
- Silver, J. M., Mc Allister, J. W., & Arciniegas, D. B. (2009). Depression and cognitive complaints following mild traumatic brain injury. *Am J Psychiatry*, 166(6), 653-661.
- Sykóva, E. (2001). Glial diffusion barriers during aging and pathological states. *Prog Brain Res*, 132, 339-363.
- Szymocha, R., Akaoka, H., Dutuit, M., Malcus, C., Didier-Bazes, M., Belin, M.F. & Giraudon, P. (2000). Human T-cell lymphotropic virus type 1-infected T lymphocytes impair catabolism and uptake of glutamate by astrocytes via Tax-1 and tumor necrosis factor alpha. *J Virol*, 74,6433-6441.
- Torp, R., Lekieffre, D., Levy, L.M., Haug, F.M., Danbolt, N.C., Meldrum, B.S. & Ottersen, O.P. (1995). Reduced postischemic expression of a glial glutamate transporter, GLT-1, in the rat hippocampus. *Exp Brain Res*, 103,51-58
- Wait, J.W. & Schoeman, J.F. (2010). Behaviour profiles after tuberculous meningitis. *J Trop Pediatr*, 56, 166-171.
- Wechsler, D. (Ed.). (2004). *Wechsler Adult Intelligence Scale – third edition, WAIS-III NI, Swedish version*. Stockholm: Pearson Assessment.
- Whelan-Goodinson, R., Ponsford, J., & Schönberger, M. (2009). Validity of the hospital anxiety and depression scale to assess depression and anxiety following traumatic brain injury as compared with the structured clinical interview for DSM-IV. *J Affect Disorder*. 114, 94-102
- Yi, J.H., Pow, D.V. & Hazell, A.S. (2005). Early loss of the glutamate transporter splice-variant GLT-1v in rat cerebral cortex following lateral fluid-percussion injury. *Glia*, 49,121-133.
- Yudkoff, M., Nissim, I., Daikhin, Y., Lin, Z.P., Nelson, D., Pleasure, D. & Erecinska, M. (1993). Brain glutamate metabolism: neuronal-astroglial relationships. *Dev Neurosci*, 15,343-350.
- Zschocke, J., Bayatti, N., Clement, A.M., Witan, H., Figiel, M., Engele, J. & Behl, C. (2005). Differential promotion of glutamate transporter expression and function by glucocorticoids in astrocytes from various brain regions. *J Biol Chem*, 280,34924-34932.



Essential Notes in Psychiatry

Edited by Dr. Victor Olisah

ISBN 978-953-51-0574-9

Hard cover, 580 pages

Publisher InTech

Published online 27, April, 2012

Published in print edition April, 2012

Psychiatry is one of the major specialties of medicine, and is concerned with the study and treatment of mental disorders. In recent times the field is growing with the discovery of effective therapies and interventions that alleviate suffering in people with mental disorders. This book of psychiatry is concise and clearly written so that it is usable for doctors in training, students and clinicians dealing with psychiatric illness in everyday practice. The book is a primer for those beginning to learn about emotional disorders and psychosocial consequences of severe physical and psychological trauma; and violence. Emphasis is placed on effective therapies and interventions for selected conditions such as dementia and suicide among others and the consequences of stress in the workplace. The book also highlights important causes of mental disorders in children.

How to reference

In order to correctly reference this scholarly work, feel free to copy and paste the following:

Lars Rönnbäck and Birgitta Johansson (2012). Long-Lasting Mental Fatigue After Recovery from Meningitis or Encephalitis - A Disabling Disorder Hypothetically Related to Dysfunction in the Supporting Systems of the Brain, Essential Notes in Psychiatry, Dr. Victor Olisah (Ed.), ISBN: 978-953-51-0574-9, InTech, Available from: <http://www.intechopen.com/books/essential-notes-in-psychiatry/long-lasting-mental-fatigue-after-recovery-from-meningitis-or-encephalitis-a-disabling-disorder>

INTECH

open science | open minds

InTech Europe

University Campus STeP Ri
Slavka Krautzeka 83/A
51000 Rijeka, Croatia
Phone: +385 (51) 770 447
Fax: +385 (51) 686 166
www.intechopen.com

InTech China

Unit 405, Office Block, Hotel Equatorial Shanghai
No.65, Yan An Road (West), Shanghai, 200040, China
中国上海市延安西路65号上海国际贵都大饭店办公楼405单元
Phone: +86-21-62489820
Fax: +86-21-62489821