Cognitive Fatigue

Iris-Katharina Penner, P. Flachenecker, and H. Meißner

1 Introduction

Contrary to earlier assumptions that MS fatigue is a unidimensional construct that can be captured by scales quantifying severity (e.g., Krupp et al. 1989; Schwartz et al. 1993), there is at least agreement at the symptom level that fatigue may manifest physically and/or cognitively. Chalder et al. (1993) were among the first to attempt to map this distinctiveness in a fatigue scale that captures both components. Most commonly, patients can be observed complaining of both physical and cognitive fatigue, albeit to varying degrees. The previous chapter dealt exclusively with motor fatigue and fatigability. The following chapter will focus on the cognitive manifestation of the symptom.

2 Definition of Cognitive Fatigue

As already explained in Chap. 2, a comprehensive and uniform definition of fatigue proves to be difficult, since, similar to pain, it is a phenomenon subjectively perceived by the individual, which largely eludes direct observation and thus objective recording and quantification. Detailed knowledge of the nature and manifestation is therefore based exclusively on reports from affected patients. In the case of cognitive fatigue, these patients complain of a lack of mental energy, which prevents them from carrying out their usual activities of daily life and, in particular, severely

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restricts them in their professional life. The more mentally demanding the occupation, the more stressful the negative impact on working life is experienced by those affected.

As with motor fatigue, the symptoms of cognitive fatigue vary according to the time of day, with a marked worsening in the afternoon and during evening hours (Comi et al. 2001; Krupp et al. 1988) and can also be triggered or intensified by stress and heat (Comi et al. 2001). Cognitive fatigue can be distinguished from normal mental daytime fatigue by the fact that it occurs unexpectedly and without any direct external correlate (such as hours of PC work or other mental activities requiring concentration and stamina) with severity and intensity that acutely prevents patients from performing their usual tasks. Cognitive fatigue is one of the leading symptoms of so-called central fatigue. Central fatigue is understood as the inability to initiate and/or maintain attentional performance ("mental fatigue") and physical activities ("physical fatigue") that require a high degree of self-motivation (Chaudhuri and Behan 2000).

While motor fatigue has been repeatedly examined by numerous imaging studies (e.g., Filippi et al. 2002; Roelcke et al. 1997), the understanding of the cognitive fatigue component can still be described as limited in comparison. This may be mainly due to the difficulty of distinguishing cognitive fatigue from a purely cognitive problem in the sense of impaired cognitive performance and to attach it to an external criterion. In the past, there were two different conceptualizations. In the first, cognitive fatigue was understood as a decrease in performance over a longer period of time, for example, in the course of a working day. However, there is little clinical evidence for this type of definition, as it has not been possible to map it reliably and objectively (DeLuca 2005). The second defined cognitive fatigue as a decline in performance during acute yet "sustained mental effort" (Schwid et al. 2003). This latter conceptualization is what we now refer to as "cognitive fatigability." In contrast to cognitive fatigue, which is purely a matter of self-perception and self-assessment on the part of the patient, cognitive fatigability describes the measurable and thus objectifiable decline in the patient's mental performance (Kluger et al. 2013).

3 Neuroanatomical Correlates of Cognitive Fatigue

As mentioned earlier, *central* fatigue is characterized by a loss of function in physical and/or mental tasks that require self-motivation and internal stimulation, in the absence of cognitive deficits or motor weakness. Chaudhuri and Behan (2000) postulated that dysfunction in the basal ganglia area was responsible for the occurrence of *central* fatigue. The authors based their assumption on the results of DeLong and Georgopoulos (1981), who were the first to describe two functionally distinct processing loops that connect the basal ganglia with the neocortex. One of them is of a purely motor nature ("motor loop"), whereas the other is of a complex, associative nature ("complex or association loop"). The latter loop receives input from the cortical association areas via the caudate nucleus, and the basal ganglia in turn project to the prefrontal cortex. A non-motor processing route between the basal ganglia, thalamus, and frontal cortex, in addition to the projection to the motor cortex, was confirmed in subsequent studies (e.g., Alexander and Crutcher 1990).

Stahl (1988) went one step further in his work and proposed to divide the basal ganglia into a neurological (motor), a psychological (cognition), and a psychiatric (emotion) part. In his model, the putamen is considered to play a crucial role in extrapyramidal motor disorders, while the connection from the caudate nucleus to the dorsolateral prefrontal cortex, as well as the ventral striatopallidal system, and here, in particular, the nucleus accumbens, are more associated with cognitive and behavioral syndromes. The connection between the caudate nucleus and the dorsolateral prefrontal cortex (= psychological part of the basal ganglia) has been shown to be a major switch point in Parkinson's disease (PD, Fuster 1989), in which the occurrence of *central* fatigue is common. A direct link between basal ganglia integrity and motivational, self-initiated processes receives clinical evidence from patients with akinesia (Denny-Brown 1962), which can be considered the most severe form of an unmotivational state. *Central* fatigue can be attributed, according to the foregoing, at least in part to a disturbed motivational component, the essential origin of which appears to lie in the dysfunction of the basal ganglia.

In relation to fatigue in MS patients, hypometabolism in the basal ganglia and frontal cortex was already discussed in the older PET literature as possible causal factor of fatigue (Roelcke et al. 1997). The results of subsequent imaging studies supported the hypothesis of a strong involvement of the basal ganglia, thalamus, and prefrontal cortex in the context of MS fatigue. The hypothesis that fatigue results from changes in distinct areas of the CNS was also functionally corroborated by the results of an fMRI study (Filippi et al. 2002). MS patients with severe physical fatigue symptoms showed a decrease in activation in regions including the thalamus involved in the planning and execution of motor actions during a simple motor task. A limitation of this study is that only physical fatigue was considered.

A paper by DeLuca et al. (2008) aimed to map the functional neuroanatomical correlates of *cognitive* fatigue. Starting from the idea that cognitive fatigue is defined as the inability to sustain a mental effort over a longer period of time, 15 MS patients and 15 healthy controls were studied while performing a modified version of the Symbol Digit Modalities Test (mSDMT [Rypma et al. 2006]) using fMRI. Contrary to imaging findings for motor fatigue, where both metabolically and functionally a decrease in activation was found in brain regions discussed as critical for fatigue (mainly frontal cortex, basal ganglia, thalamus), DeLuca et al. reported an increase in activation in these critical regions for cognitive fatigue. The authors related their results to those found in imaging studies of cognition in MS and argued that the additional recruitment of brain areas to perform a cognitive task reported in these studies (e.g., Mainero et al. 2004; Penner et al. 2003) does not represent compensatory or plasticity processes, but rather cognitive fatigue. This argumentation seems questionable against the background of the numerous existing imaging results on motor fatigue and cognition in MS and is furthermore refuted by the results of another fMRI study on motor and cognitive fatigue in MS (Lange et al. 2006). Rather, it appears that the operationalization of cognitive fatigue must be critically questioned once again. A study by Bailey et al. (Bailey et al. 2007), who focused on MS patients in an advanced stage of progressive MS, found little evidence for objective signs of cognitive fatigue (defined as a decline in working memory over time). Subjective measures of fatigue, using a simple rating scale to the question, "How fatigued do you feel right now?" (response continuum from 0 = not at all to 8 = extremely) was collected multiple times during performance of the working memory task showed an increase over testing for both patients and healthy controls, which was more pronounced for patients in the higher working memory load condition. Nevertheless, correlation analyses between subjective fatigue statements and the cognitive measures (conceptualized as a measure of cognitive fatigue) did not yield significant results in the patient cohort either. This result illustrates that a decline in cognitive performance over time is not necessarily due to cognitive fatigue and that other factors, such as motivation and affect, should be taken into account.

However, the importance of the basal ganglia and prefrontal cortex in the context of MS fatigue was reconfirmed in a recently published study (Jaeger et al. 2019). In this MRI study, MS fatigue was shown to be characterized by impaired connectivity of the striatum with the sensorimotor, attentional, and reward networks. The superior ventral striatum was here thought to play a key role in MS fatigue.

4 Cognitive Fatigue and Cognition

The concept of cognitive fatigue as a loss of mental performance over time was reconsidered by results that reported no or only very weak relationships between the extent of subjective fatigue and cognitive performance (e.g., Bailey et al. 2007; Paul et al. 1998). Krupp and Elkins (2000) investigated the relationship between the objectifiable cognitive performance of MS patients over a test period of 4 h and the subjectively experienced fatigue by the patients. Again, no demonstrable relationship was found between the two variables. Findings from our own work (Penner et al. 2009) also suggest only a weak relationship between objective cognitive performance and cognitive fatigue. In this extensive validation study of a new fatigue questionnaire (FSMC—Fatigue Scale for Motor and Cognitive Functions), which was carried out multicentrally on a collective of 309 MS patients, only a weak relationship (in view of the low correlation coefficients) between cognitive fatigue and two neuropsychological tests, which primarily assess information processing speed, attention-concentration ability and working memory (SDMT, PASAT), could be demonstrated. All other neuropsychological instruments for visual-spatial and verbal short- and long-term memory as well as for word fluency (executive functions) showed no significant correlation with cognitive fatigue.

5 The Role of Attention in the Diagnosis of Fatigue

In addition to the subjective assessment of fatigue with the help of questionnaires and a detailed anamnesis, the examination of attention has become more and more established in fatigue diagnostics in recent years. Attentional functions are understood as basic functions involved in almost any intellectual or practical demand. They are relatively independent of control strategies that can be used to compensate for fatigue and thus represent an objective parameter for the assessment of fatigue. Attention is not a unidimensional phenomenon but is categorized according to intensity and selectivity aspects (Van Zomeren and Brouwer 1994), which in turn can be assigned to different components and functional networks (Fig. 1). The aspect of attentional intensity can be understood as a state of general alertness and cognitive activation. This comprises the domains of alertness (tonic, phasic), sustained attention, and vigilance, which represent basic processes of short- and longer-term attentional activation or the maintenance of an activation. The dimension of attentional selectivity, on the other hand, is subdivided into the components of selective or focused attention, the spatial orientation of attention, mental flexibility, and the ability to divide attention.

Based on this classification, the *neuropsychological* examination of the intensity of attention for the objectification of cognitive fatigue is of particular importance (Fig. 1).

In a first systematic study with 57 MS patients, a correlation between subjectively experienced fatigue, measured with the WEIMuS questionnaire, and the intensity of attention could be demonstrated (Meissner et al. 2007). For this

Dimension	Domain	Functional Network
Intensity	Alertness: intrinsic, tonal, phasic Sustained attention Vigilance	Brain stem portion of formatio reticularis, in particular noradrenergic core areas, dorsolateral prefrontal and inferior parietal cortex oft the right hermisphere, intralaminary and reticular thalamic nuclei, anterior part of the cingulate gyrus
Selctivity	Selective oder focused attention	Dorsolateral and inferior frontal cortex, in particular of the left hemisphere (inhibition ?), fronto-thalamic connections to the nucleus reticularis of the thalamus, anterior cingulum
	Visual-spatial selective attention, mental flexibility	Inferior parietal cortex clear right (disengage), superior colliculi (shift), posterior-lateral thalamus, especially pulvinar (engage)
	Divided attention	Prefrontal cortex (bilateral), anterior sections of the cingulum

Fig. 1 Adapted from Sturm (2000): Attention dimensions and domains and functional networks

purpose, tonic alertness (test duration of about three minutes) was first tested, followed by a 15-minute measurement of sustained attention and a renewed test of tonic alertness. After this first repetition, an examination of attentional selectivity took place. The final test was another measurement of tonic alertness. Already the first examination of alertness showed a highly significant correlation of mean reaction times with WEIMuS scale scores ($r = 0.46$, $p < 0.0001$), especially with the cognitive fatigue subscale. After correction for depression, the correlation coefficient increased to 0.51 (Meissner et al. 2007). The repetitive measure depicted a further increase in reaction latencies with concurrent poorer performance on the sustained attention subtest. In contrast, there was no correlation with selective attention. Thus, at least in the patients who mainly complain of mental fatigue, there seems to be a simultaneous disturbance in the intensity of attention, but not in its selectivity aspects. This also explains the divergent results of earlier studies reported in the literature, which document a lack of correlation with various cognitive function tests. On the one hand, in these studies fatigue was predominantly assessed by the Fatigue Severity Scale (FSS), which focuses exclusively on physical aspects of fatigue, while on the other hand neuropsychological tests were used that mapped cognitive aspects such as memory or focused attention. These cognitive functions are therefore obviously unsuitable to make an objective contribution to the diagnosis of fatigue.

The results of other research groups support the reported findings on alertness. For example, Weinges-Evers et al. (Weinges-Evers et al. 2010) were able to show in 110 MS patients that the group suffering from fatigue (51.4%, defined as FSS ≥ 4.0) had significantly higher reaction times in tonic alertness than the group of patients without fatigue, while no differences between the two groups were detectable for other neuropsychological test results (visual scanning or executive control). However, this study unfortunately also used the FSS, which does not allow measurement of cognitive fatigue. Also, in a study by Claros-Salinas et al. tonic alertness proved to be the most sensitive test for detecting fatigue (Claros-Salinas et al. 2013). Consistent with what has been reported so far, in another study, reaction times in the alertness subtest were significantly increased in MS patients with fatigue compared to healthy controls and continued to increase after cognitive load, while in contrast they even slightly decreased in healthy controls (Neumann et al. 2014). Further evidence comes from a controlled, randomized study on the effects of intensive ergometer training (with and without an altitude chamber): Again, only attention intensity, measured with the “Alertness” subtest of the Test Battery for Attention (TAP), correlated significantly with WEIMuS scale scores. After the two-week training, there was a decrease in subjective fatigue, which was associated with improved reaction times on the attention test. Fatigue and attentional parameters were also significantly correlated at this second measurement point (Fig. 2). Along the lines of the studies presented so far, fatigue values and other tests of cognitive performance (“executive control”) did not show a significant correlation at any of the measurement points (Pfitzner et al. 2013).

Most patients complain of an increase in fatigue over the course of the day, which is why a single measurement is often insufficient, especially for questions relating

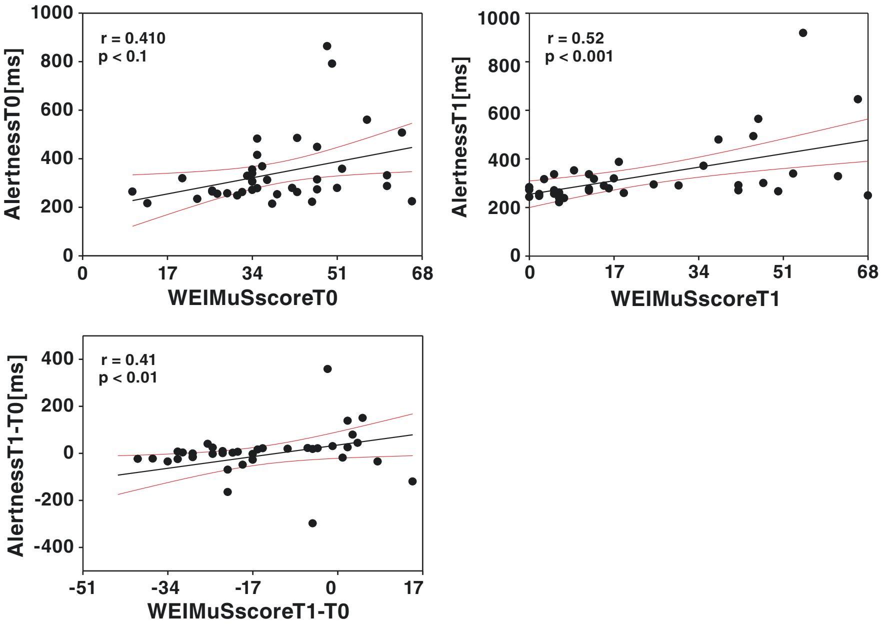

Fig. 2 Correlation between subjectively experienced fatigue (WEIMuS Score) and reaction times in the subtest "alertness" of the test battery for attention testing (TAP) before (T0) and after (T1) a two-week ergometer training. The graph below shows the reaction times of each patient against the differences in the WEIMuS scale values plotted (Pfitzner et al. 2013)

to occupational performance. In this respect, the work of Claros-Salinas et al. is worth mentioning, in which the circadian attentional performance of 76 rehabilitation patients with various neurological diseases (of which MS patients formed the etiologically largest group with 37 participants) was investigated and compared with the findings of 76 employed, brain healthy control subjects (Claros-Salinas et al. 2010, 2012). For this purpose, different subtests of the attentional test battery (Alertness, Go/Nogo, divided attention) were administered over 2 days at three defined measurement time points. In the control group, the mean reaction times in the "Alertness" subtest remained stable over the six measurements and even showed an increase in performance in the sense of a reduction in the mean reaction times in the other subtests. In the patient group, however, the mean reaction times were significantly longer. In addition, over the course of the day, the mean reaction times increased in the sense of circadian deterioration, especially in the "Alertness" subtest. In case of inconspicuous findings in the morning and subjectively reported fatigue, a new test should therefore be performed in the afternoon.

In line with the findings on alertness presented so far, a review of numerous studies reports that an association with fatigue was only present for those neuropsychological tests that assessed aspects of attention intensity (alertness or vigilance) (Hanken et al. 2015). It is now well established that fatigue is at least partly caused by a specific attention impairment, but that it can also be clearly distinguished from performance in other cognitive domains.

The neuropsychological examination of attention intensity thus provides a sensitive and time-efficient way of objectively detecting cognitive fatigue symptoms. This represents a considerable improvement over a purely subjective survey by means of a questionnaire, particularly in the case of socio-medical questions such as the assessment of occupational performance. The discrepancy between the partially inconsistent results in the literature is probably due to sampling and methodological effects, among other things. For example, in previous studies fatigue was predominantly assessed by the FSS, which measures only physical fatigue. However, this is not adequately represented by testing attentional performance. On the other hand, mainly neuropsychological tests were used, which examined different cognitive aspects such as memory or visuospatial performance. These cognitive functions were also not correlated with fatigue in the studies cited above and are obviously unsuitable for making an objective contribution to fatigue diagnostics.

6 Summary

The comments on cognitive fatigue illustrate how difficult it is to define and objectively record the cognitive dimension in addition to the motor component. Based on the above-mentioned study results, it can be assumed that a dysregulation in the processing loop between the basal ganglia, thalamus, and prefrontal cortex plays a decisive role in the development and maintenance. In this context, however, motivational as well as emotional factors also seem to play a significant role. Attention tasks such as “alertness” seem to be the most suitable for operationalization. In combination with behavioral observation, comprehensive neuropsychological profiling in general and attentional performance profiling, in particular, can be used to approximate the objectification of cognitive fatigue.

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