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REVIEW PAPER

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Physical fatigue measured by functional MRI

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ABSTRACT

Introduction. Physical fatigue is a physiological condition that can be measured by functional Magnetic Resonance Imaging (fMRI).

Aim. Therefore, this work aims to present the research results currently reported in the scientific literature between the years 2014 and 2018 in the field of chronic fatigue syndrome using the functional MRI method.

Material and methods. Analysis of literature.

Results. We reviewed here the differences between temporary and chronic fatigue.

Keywords. functional MRI, physical fatigue, physiological condition, temporary and chronic fatigue

Rationale for the fMRI study

Physical fatigue is a physiological condition that is manifested in a temporary-transient decrease in the ability to work and a decrease in mobility. Chronic fatigue syndrome is a complex problem which manifests in visual impairment, heart palpitations, increased hair loss, lack of concentration, memory problems as well as frequent headaches and numbness of the hand. The above mentioned symptoms may be accompanied by many diseases of various etiology, e.g. depression, neurostemia, multiple sclerosis, or some infections.[1] The etiology of fatigue is not well understood and scientific research conducted to elucidate the mechanisms of fatigue are necessary to efficiently diagnose chronic fatigue syndrome. The fMRI technique is based on the influence of a strong magnetic field and an electromagnetic wave at a strictly defined frequency on the nucleus of chemical elements with non-zero spin. This variant of MRI is currently the key non-invasive technique for brain imaging. This technique has excellent spatial and temporal resolution and is sensitive to changes in signal strength depending on the degree of blood oxygenation. It is

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Participation of co-authors: A – Author of the concept and objectives of paper; B – collection of data; C – implementation of research; D – elaborate, analysis and interpretation of data; E – statistical analysis; F – preparation of a manuscript; G – working out the literature; H – obtaining funds

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known that levels of blood oxygenation in the brain vary depending on the activity of neurons, and these differences can be used to detect brain activity. This is due to the increased demand for energy and oxygen in the area of increased brain activity. The basis of this imaging is the so-called Blood Oxygenation-Level Dependent (BOLD) contrast that depends on the level of oxygen in the blood. fMRI has many clinical applications and is used to validate neuroimaging, and to search for brain markers in psychiatry, which makes it a technique at the borderline of clinical and experimental-methodological sciences. Blood Oxygenation-Level Dependent contrast is one of the best-known techniques of fMRI that can be used to map blood oxygenation in the brain. The use of this technique allows for identification of brain tumors and patients with epilepsy. This technique demonstrates early promise and can also play a role in providing future diagnostic and prognostic information in patients with neurological and psychiatric diseases and opens up a wide range of possibilities for chronic fatigue syndrome testing. Based on studies available in the literature, it is very likely that fatigue assessment is not possible using MRI based T_1 spin-lattice relaxation and spin-spin relaxation T_2 of water alone.[2] Fatigue, being a physiological reaction with variations in hemoglobin, can be imaged by fMRI. Fatigue is often reported by patients who have had a mild brain injury which affects the ability of people to return to work in a reasonable timeframe.[3] A study by Möller et al. subjected 10 patients with mild cognitive impairment and fatigue (5 women and 5 men) to fMRI after suffering a stroke.[3] The paradigm of the study was based on patients maintaining constant attention to a task being carried out under fMRI monitoring. This task was a response time to a visible stimulus. The research did not show any group differences regarding age, education, body weight or the consumption of caffeine on the day of the study. The authors of this study showed that patients could be identified as suffering from chronic fatigue after mild stroke compared to the control group by fMRI. Measurements of regional cerebral blood flow and quantitative mapping of joints can also provide an objective assessment of fatigue during a continuous vigilance test. As a result, the authors of this study confirmed that the fMRI technique can be used to assess chronic fatigue in patients after mild stroke.

Subjective fatigue is also a typical symptom of diseases such as multiple sclerosis, Parkinson's disease or stroke. Pardini et al.[4] examined 14 patients with multiple sclerosis by fMRI. The task that the patients were asked to do was to touch their other fingers with their thumb. The sequence was attempted at a frequency generated by a 2 Hz metronome. A force measurement was also carried out by application of a special glove adapted for this task. The obtained results showed a strong correlation between the time accuracy of the performed task and the feeling of chronic fatigue.[4] Other authors point to the potential adaptation of the brain to fatigue. Perhaps it is related to a feedback loop effect in which the brain tries to maintain the initial efficiency.[5] In many studies, authors point to activation regions affected by fatigue located in the cerebellum and frontal cortex.[4,6,7] Other studies of fatigue in patients with multiple sclerosis checked how quickly task ability was regained after deterioration resulting from the task performed initially. A total of 14 patients were subjected to a deterioration of spatial and temporal accuracy in the first part of the task consisting of a sequence of touching the other fingers with the thumb of the right hand. The second part of the study showed that after a short 5-minute rest, a return of temporal accuracy, but not spatial. After rest, the activity of activated regions obtained values similar to baseline values except in the amygdala by fMRI. This suggests that patients that have been in a state of fatigue from the beginning of the task showed an increased BOLD signal in subcortical structures that are known to be recruited in healthy patients only when dealing with fatigue to improve motor performance. On the basis of research it can be said that rehabilitation treatment brings much better results than pharmacological treatment.[8] Results have been presented that the rehabilitation of people with multiple sclerosis reporting only fatigue symptoms should be the treatment of choice. It should be noted that only a small group of people will feel the benefits of such treatment. The study included a small group of people and the extent of efficacy in other subgroups of multiple sclerosis patients is unknown. It seems that the above observations may be related only to the initial stage of the disease. The next steps should take into account future consequences of the choice or resignation from pharmacological treatment in this regard. Interesting research results were presented in 2015 by Hampson and colleagues.[9] Twenty three patients were examined after recovery from breast cancer. Visible persistent fatigue associated with breast cancer was associated with reduced sleep quality, cognitive impairment, and ultimately depression. These studies from 2015 appear to be one of the first fMRI applications in the analysis of fatigue in patients with breast cancer. As a result of the analysis, an area in the frontal lobe was identified using fMRI analysis techniques which may be a potential region to track fatigue in patients. Higher fatigue is also indicated in the parietal region of cancer patients during fMRI tests.[6] Increased fatigue coexists with worsening physical functioning and cognitive impairment. With such an analysis, the effects of oncological therapy should be taken into account, which in itself has a great impact on the emotional and physical state of the patient where fatigue is just one of many side effects. In recent years, populations have access to mod-

Table 1. Background of Imaging procedures and Image processing

References	Imaging procedures	Image processing
Frank S. *et al.* 2010[11]	blood oxygen-level dependent (BOLD) fMRI data were obtained by using a 3.0 T MRI scanner	analysis of the fMRI data was performed with Statistical Parametric Mapping software (SPM5)
Vocks S. *et al.* 2011[12]	BOLD contrast images were acquired using an echo-planar (EPI) technique; images were acquired using a 1.5 T MRI scanner; additionally an MRI compatible finger clip pulse oximeter was used to measure heart rate	pre-processing and statistical analyses of the fMRI data were performed using the Statistical Parametric Mapping software (SPM5)
Chin SH *et al.* 2018[13]	fMRI data were acquired using an echo planar imaging sequence; T1-weighted MPRAGE scan was also collected using a 3.0 T MRI scanner	all structural and functional raw data images were converted to NIfTI format using the dcm2nii converter (Rorden & Brett, 2005). Freesurfer (autorecon1) was used for structural image preprocessing and FMRIB Software Library (FSL; Version 6.00, Oxford, UK) for functional image preprocessing and analysis; the FEAT tool in FSL was used to analyze the fMRI data
Picchioni D. *et al.* 2008[14]	(BOLD) fMRI was acquired on a 3.0 T MRI scanner; single-shot echo-planar images were collected from 28 oblique-axial slices covering most of the brain; 3D T1-weighted MPRAGE images were collected	fMRI analysis was performed using IDL 6.2 (ITT visual information solutions, Boulder, CO, USA), Statistical Parametric Mapping software (SPM2) and Analysis of Functional Neuro Images (AFNI); IDL and SPM2 were used for pre-processing the data while AFNI was used for additional pre-processing and for the statistical analyses
Wang Y. *et al.* 2016[10]	images were acquired in a 3.0 T MRI scanner; functional data comprised 1008 vol acquired with T2*-weighted gradient echo planar imaging sequences	all preprocessing steps were carried out using the Data Processing Assistant for Resting-State fMRI V2.0; after preprocessing, Statistical Parametric Mapping software (SPM12) was used to analyze the imaging data
Lange G. *et al.* 2005[15]	imaging was performed on a 1.5 T MRI scanner; initial T1-weighted sagittal localizer was acquired to determine the location of the MR images; T1-weighted axial images encompassing the whole brain were acquired	the functional neuroimaging data were analyzed using Statistical Parametric Mapping software (SPM99)
Porubská K. *et al.* 2006[16]	fMRI data were obtained using a 1.5 T MRI scanner; Functional T2*-weighted images were acquired in axial orientation using echo-planar imaging (EPI)	preprocessing and statistical analyses were carried out using Statistical Parametric Mapping software (SPM2)
van Duinen H. *et al.* 2007[17]	3.0 T MRI scanner was used; fMRI data were acquired using an echo planar imaging sequence; additionally T1-weighted anatomical images of the entire brain were obtained	the fMRI data were preprocessed using Statistical Parametric Mapping software (SPM2)
Jacobson A. *et al.* 2010[18]	T1-weighted whole brain MP-RAGE sequence were performed using 3.0 T MRI scanner	analysis of Functional Neuro Images (AFNI) software was used in all of the processing and analyses of the structural and functional data
Tsai P-J. *et al.* 2014[19]	MRI data were acquired using a 3.0 T scanner; T1-weighted anatomical images (3D-MPRAGE) were acquired prior to functional scans for geometric localization	all fMRI data were preprocessed by Statistical Parametric Mapping (SPM5)
Thomas R.J. 2005[20]	imaging was performed on a 3.0 T MRI scanner; a gradient echo T2*-weighted sequence was used to obtain BOLD contrast data; high resolution T1-weighted scan was used as an intermediate step for functional overlays prior to transformation into the threedimensional space	preprocessing included motion correction, spatial smoothing, linear trend removal and temporal high-pass filtering using the Brain Voyager 2000 (Brain Innovation, Maastricht, The Netherlands) software package

ern electronic entertainment technologies, of which one of the most important is three-dimensional (3D) tv technology. For example, when watching television programs, the deoxy- and oxyhemoglobin concentrations are significantly increased, which is associated with increased blood supply to the brain. Increasing the blood supply to the brain also at the same time indicates an increased energy demand. In addition, the metabolic rate drops significantly due to fatigue.[7] Researchers examined 40 participants randomly selected who were to

Table 2. Background of Imaging procedures and Image processing

References	Aim	Methods	Results and Conclusions
Frank S. *et al.* 2010[11]	Explanation of the neural basis of human eating behavior using fMRI	the modulating effects of calorie content and hunger on food processing related brain activity were study using fMRI	the calorie content of food pictures modulates the activation of brain areas related to reward processing and even early visual areas
Vocks S. *et al.* 2011[12]	assessment hunger- and satiety-dependent alterations in the gustatory processing of stimulated with food in anorexia nervosa were study using fMRI	females in hunger condition and in satiety condition (females with restricting-type anorexia nervosa and healthy females) drank chocolate milk and water via a tube in a blocked design during image acquisition	neuronal responses evoked by gustatory stimulation differ depending on hunger and satiety; activations located in the amygdala and in the extra striate body area might reflect fear of weight gain
Chin SH *et al.* 2018[13]	influence of self-reported hunger in behavioral and fMRI food-cue reactivity (fMRI-FCR)	required rating images of food and matched objects were presented during fMRI-FCR study; hunger, satiety, thirst, fullness and emptiness were measured pre- and post-scan	few self-reported hunger, satiety or related constructs appear to moderate fMRI-FCR in certain brain regions such as the amygdala and the orbitofrontal cortex; this results suggest that controlling for these constructs in the analyses of fMRI data derived from food-cue reactivity paradigms is likely to have minimal to no influence on the overall interpretation of findings in fMRI-FCR studies
Picchioni D. *et al.* 2008[14]	ascertainment differences in regional brain activity between stage-1 sleep immediately following wake and immediately preceding stage-2 sleep	brain activity between the first 30 s of stage 1 (early stage 1), the last 30 s of stage 1 (late stage 1), and isolated wake were compared; data were collected during daytime fMRI sessions with simultaneous EEG acquisition	activity in anatomically identifiable, volumetric brain regions exhibit differences during stage-1 sleep that would not have been detected with the EEG
Wang Y. *et al.* 2016[10]	restraint status modulated attentional bias to food cues and the different neural activations associated with these responses were study using fMRI	fMRI study was conducted in restraint eaters and unrestraint eaters exposed to high/low-energy food and neutral images while performing a two-choice oddball task	restrained eaters responded more quickly to high-energy food images than to neutral and low-energy food images; restrained eaters showed faster reaction times, hyperactivation in a much wider array of reward (e.g., insula/ orbitofrontal cortex), attention (superior frontal gyrus) and visual processing (e.g., superior temporal gyrus) regions, and hypo-activation in cognitive control areas (e.g., anterior cingulate) in response to high-energy food cues; potential neural bases of restrained eaters may help clarify why dieting to lose or maintain weight is so often unsuccessful
Lange G. *et al.* 2005[15]	BOLD fMRI study of verbal working memory; study of cognitive complaints in Chronic Fatigue Syndrome (CFS)	BOLD signal changes between Controls and individuals with CFS who had documented difficulties in complex auditory information processing (Study 1) and those who did not (Study 2) in response to performance on a simple auditory monitoring and a complex auditory information processing task were compared in fMRI study	individuals with CFS are able to process challenging auditory information as accurately as Controls but utilize more extensive regions of the network associated with the verbal working memory system; individuals with CFS have to exert greater effort to process auditory information

Porubská K. *et al.* 2006[16]	the neuroanatomical correlates of eating behavior and its influences on the central nervous processing in humans were studied	fMRI technique was used to measure the cortical activation in lean healthy humans during visual stimulation with food-related and nonfood pictures after a fasting period of at least 5 h	the food stimuli elicited a significantly greater activity in the left orbitofrontal cortex and the insular/opercula cortex bilaterally with a stronger focus on the left side; ratings of appetite during the presentation of food-related stimuli modulated the activity in the insula bilaterally, the left operculum and the right putamen
van Duinen H. *et al.* 2007[17]	investigation effects of motor fatigue on brain activation in humans using fMRI	brain activation that correlated with muscle activity during brief contractions at different force levels and sustained contractions inducing motor fatigue were studied using fMRI; studied changes in brain activation due to motor fatigue over time; investigated cross-over effects of fatigue by comparing brain activation before and after the fatiguing condition during simple and high-order motor tasks using fMRI	several motor areas in the brain showed increased activity with increased muscle activity, both during force modulation and motor fatigue; after fatigue increased activation in orbitofrontal areas was found; the activity in the supplementary motor area and frontal areas is affected by motor fatigue
Jacobson A. *et al.* 2010[18]	examination age-related changes in gustatory processing during hedonic assessment	caffeine, citric acid, sucrose, and NaCl were administered orally during two event-related fMRI sessions, one during hunger and one after a pre-load	increased activity of the insula was seen in both age groups during hunger; hunger and satiety differentially affected the hemodynamic response, resulting in positive global activation during hunger and negative during satiety in both age groups; in a state of hunger, the frequency and consistency of positive activation in gustatory and reward processing regions was greater in older adults
Tsai PJ. *et al.* 2014[19]	the sleep regulation a network-specific process and the awakening state dependent on the previous sleep stages were studied	simultaneous EEG and fMRI recordings healthy male participants, along pre-sleep, nocturnal sleep and awakening were studied	the regional specificity and the stage effect were verified in support of the local awakening concept; sleep regulation leads to the reorganization of brain networks upon awakening
Thomas R.J. 2005[20]	to demonstrate dynamic changes in cerebral functional activation during a working memory task in a state of severe excessive daytime sleepiness	fMRI was used to map cerebral activation during the performance of a 2-back verbal working memory task; scans were performed, until the subjects felt they could not continue	fatigue in the executive cortical network may be demonstrated by a progressive reduction in regional cerebral activation across scans, which may be prevented by stimulant use
Wirsich J. *et al.* 2017[21]	resting-state fMRI to explored the whole brain functional connectivity effects of modafinil, donepezil and memantine in normal and sleep-deprived brain states in order to reveal the functional subnetworks modified by these medications, while controlling for sleep stages extracted from a simultaneous EEG recording	simultaneous EEG-fMRI in order to investigate the effects of donepezil and memantine before and after sleep deprivation (SD); the SD approach has been previously proposed as a model for cognitive impairment in healthy subjects	a network linked to sleep is interacting with sleep deprivation but not with medication intake; donepezil induced whole brain connectivity alterations forming a network separated from the changes induced by sleep and SD; a result shows possibilities to check for the validity of pharmacological resting-state analysis of the tested medications without the need of taking into account the subject specific vigilance

watch 3D or 2D television chessboards. The stimulus of the study was 2 hours in duration. Analysis of the results confirmed that subjects watching 3D TV had visual fatigue. This was also confirmed by an analysis of fMRI images showing that long-term 3D TV viewing leads to larger changes in activated brain regions than those in a 2D TV viewing group. In a paper from 2016, the existence of a mechanism was postulated that compensates for fatigue in the brain and which attempts cognition. [10] Understanding the compensation mechanism can be helpful in understanding the phenomenon of fatigue itself and to therapeutic actions. In their research, they indicated the frontal lobe as the region responsible for the compensation mechanism. At the moment, research is being carried out in several centers concerning the mechanisms of fatigue. Understanding the mechanism of fatigue in the brain by fMRI and the postulated compensating mechanism will be very important for improvements in the quality of life for patients suffering from chronic fatigue syndrome.

Conclusion

Functional MRI has many clinical applications and is used to validate neuroimaging, and to search for brain markers in psychiatry, which makes it a technique at the borderline of clinical and experimental-methodological sciences. Blood Oxygenation-Level Dependent contrast is one of the best-known techniques of fMRI that can be used to map blood oxygenation in the brain. The use of this technique allows for identification of brain tumors and patients with epilepsy. This technique demonstrates early promise and can also play a role in providing future diagnostic and prognostic information in patients with neurological and psychiatric diseases and opens up a wide range of possibilities for chronic fatigue syndrome testing.

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