

# A wireless body measurement system to study fatigue in multiple sclerosis

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## A wireless body measurement system to study fatigue in multiple sclerosis

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### Abstract

Fatigue is reported as the most common symptom by patients with multiple sclerosis (MS). The physiological and functional parameters related to fatigue in MS patients are currently not well established. A new wearable wireless body measurement system, named Fatigue Monitoring System (FAMOS), was developed to study fatigue in MS. It can continuously measure electrocardiogram, body-skin temperature, electromyogram and motions of feet. The goal of this study is to test the ability of distinguishing fatigued MS patients from healthy subjects by the use of FAMOS. This paper presents the realization of the measurement system including the design of both hardware and dedicated signal processing algorithms. Twenty-six participants including 17 MS patients with fatigue and 9 sex- and age-matched healthy controls were included in the study for continuous 24 h monitoring. The preliminary results show significant differences between fatigued MS patients and healthy controls. In conclusion, the FAMOS enables continuous data acquisition and estimation of multiple physiological and functional parameters. It provides a new, flexible and objective approach to study fatigue in MS, which can distinguish between fatigued MS patients and healthy controls. The usability and reliability of the FAMOS should however be further improved and validated through larger clinical trials.

Keywords: fatigue, multiple sclerosis, physiological and functional parameters, wireless monitoring system

(Some figures may appear in colour only in the online journal)

## 1. Introduction

Multiple sclerosis (MS) is an incurable, chronic and unpredictable demyelinating disease in which primarily the myelin sheaths covering the axons in the central nervous system are damaged and axonal loss can also occur. MS affects the ability of nerve cells in the brain or spinal medulla to communicate with other cells, which leads to a broad range of signs and symptoms. During disease activity and disease progression, MS patients commonly complain about symptoms such as the loss of function or sensation in the limbs, the loss of bowel or bladder control, sexual dysfunction, blindness, the loss of balance, pain, cognitive dysfunction, emotional changes and fatigue (Mohr and Cox 2001). Among these, fatigue is reported as the most common symptom by MS patients (Freal *et al* 1984, Krupp *et al* 1988, 1989, Fisk *et al* 1994).

Fatigue in MS is categorized by its etiology. It may be primary fatigue, which is primarily related to the disease mechanisms in the central nervous system, such as demyelination, axonal loss or inflammation. It may also be caused by secondary non-specific disease-related factors, which are in this case described as secondary fatigue. In general, the distinction between primary and secondary fatigue for individuals is very complex. Fatigue may have a complex origin best explained from a multifactorial perspective rather than a single mechanism (Kos *et al* 2008).

Many studies attempted to explain fatigue from different pathophysiological mechanisms. Most of these studies concentrated on the disease mechanisms that could explain primary fatigue. Different devices or techniques, such as magnetic resonance imaging (MRI), functional MRI, positron emission tomography and electrophysiological measurements, combined with self-reported fatigue questionnaires, have been used to study the mechanism of primary fatigue. Various anatomical brain areas have been found having associations with MS fatigue. Comparably fewer studies explained fatigue from another perspective. They focused on secondary fatigue and tried to find fatigue contributors besides the disease mechanisms. It has been proven that sleep disorder, severe pain, use of medication, and some psychological factors such as depression, anxiety and stress may contribute to fatigue in MS (van Kessel and Moss-Morris 2006, Kos *et al* 2008). However, whether other primary or secondary factors are related to MS fatigue is still unclear, and unexplained fatigue is very often simply considered as primary fatigue.

Frequently applied techniques such as MRI or fMRI have provided significant contributions to the study of fatigue, but these measurements are affected by several limitations. They do not permit long-term monitoring (e.g., 24 h) and the subject under scanning is not free to move. Due to these limitations, none of the previous studies with MRI or fMRI (White *et al* 2004, Rocca *et al* 2007, Tartaglia *et al* 2008, DeLuca *et al* 2008, Rocca *et al* 2009) involved any complex task assigned to the subjects, especially complex physical tasks. Only a few studies evaluated fatigue-related physiological and functional parameters among MS patients. An early study reported reduced vagal tone in MS patients by investigating the physiological response to treadmill exercise, but the authors did not clarify whether MS patients were fatigued (Reisman *et al* 1991). Some studies indicated autonomic dysfunction in fatigued MS patients (Keselbrener *et al* 2000, Flachenecker *et al* 2002); however, another study reported inconsistent findings (Merkelbach *et al* 2001). Taken together, MS fatigue-related physiological and functional parameters are currently not well established. All the studies were performed in a clinical setting, where the participants may perform differently from their normal daily settings. The currently used techniques are not suitable for continuous monitoring of patients at home. Consequently, a new measurement system is required for the study of fatigue in MS.

Along with the fast development of communication technologies, a wearable sensor-based system has become the most promising concept for patient monitoring. It has attracted attention both in academia and industry in the last few years. Wireless body sensor networks, for example, are wearable healthcare systems that typically consist of a set of intelligent, miniaturized and low-power sensor nodes (Hao and Foster 2008). Various wearable sensor-based health monitoring systems have been developed in several studies. According to Pantelopoulos and Bourbakis (2010) survey on wearable sensor-based systems, different communication modules and signals were implemented and measured in these systems for different applications. For instance, in the CodeBlue project (Shnayder *et al* 2005), a system based on ZigBee, which can monitor electrocardiogram (ECG), electromyogram (EMG) and oxygen saturation, was designed for fast response scenarios. Alerts will be raised when the vital signs of patients fall outside the normal range. In another project, HeartToGo aimed at cardiovascular disease prevention and detection, and a system to measure ECG signal and activities based on Bluetooth bio-sensors and cellphone was developed (Jin *et al* 2009, Oresko *et al* 2010). Systems for other applications have also been considered (Venkatasubramanian *et al* 2005, Gyselinckx *et al* 2006, Jeong *et al* 2009, Chi and Cauwenberghs 2010); however, none of these projects aimed at studying fatigue in MS patients. Therefore, we have developed a wearable wireless measurement system, named Fatigue Monitoring System (FAMOS), which is a signal acquisition and analysis system for long-term continuous estimation of major physiological and functional parameters, including ECG, EMG, body-skin temperature and motion. The goal of this study is to test whether fatigued MS patient can be distinguished from healthy subjects by implementing this wearable wireless measurement system. Compared with current clinical health monitoring systems, the FAMOS releases patients from the hospital. It can perform long-term monitoring of a range of physiological and functional parameters during cognitive and functional tests, as well as during daily living. Furthermore, it also permits remote monitoring of patients. This paper presents the realization of the measurement system including the design of both hardware and dedicated signal processing algorithms. In addition, a pilot study was performed by means of the FAMOS. Twenty-six participants were recruited and tested for approximately 24 h over day and night. A set of cognitive and functional tests were included. The results of this pilot study are reported.

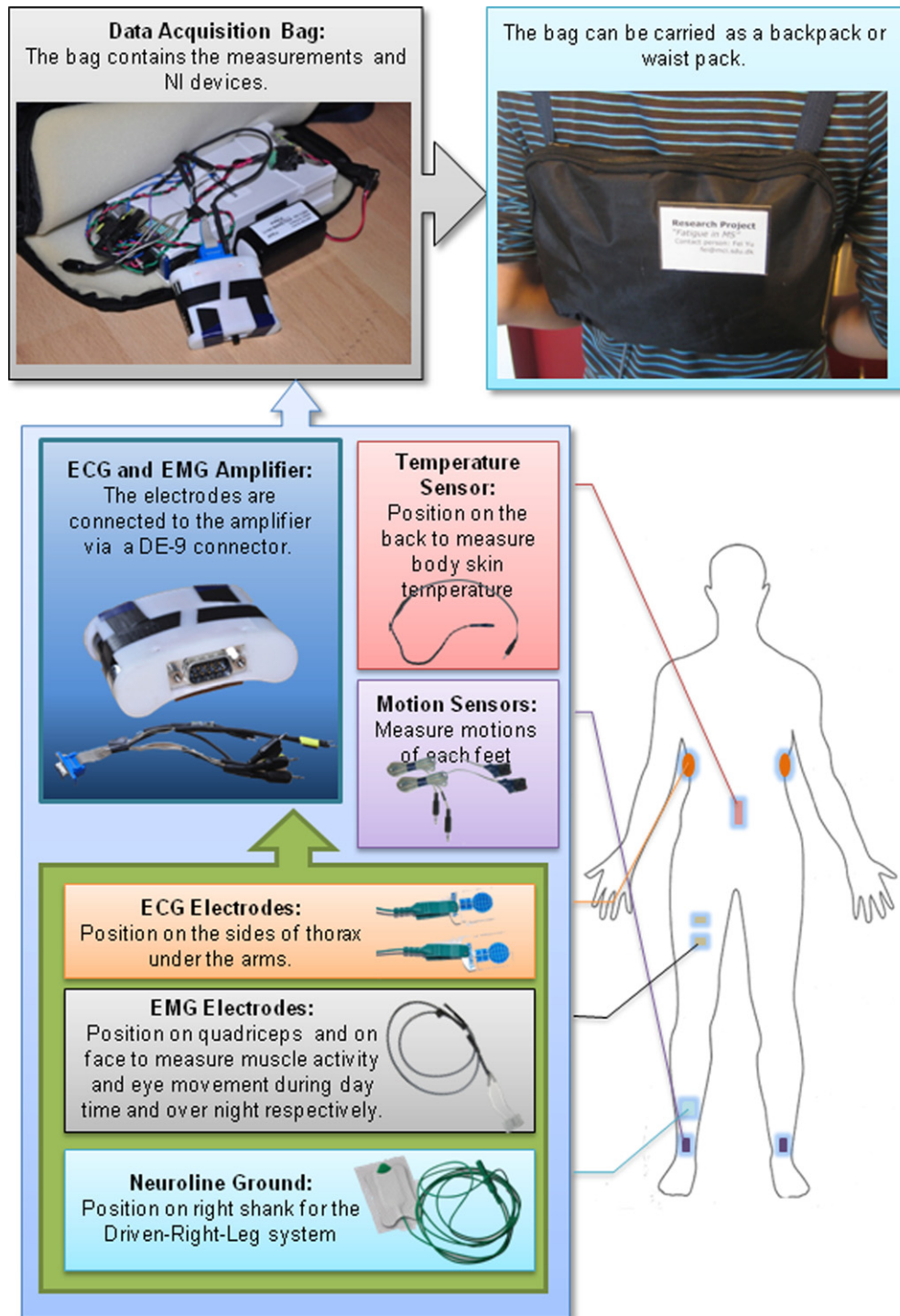
## 2. Fatigue monitoring system

Figure 1 depicts the new FAMOS prototype together with the sensor positions. All the electronics for signal acquisition, conditioning and communication are placed in a bag, which can be carried as a backpack or waist pack. The signals are transferred continuously to a laptop via a wireless router and are saved as txt files for data analysis.

A National Instruments (NI, Austin, TX) wireless data acquisition device WLS-9205 is used to acquire all the signals. It supports IEEE 802.11b/g wireless and Ethernet communication interfaces.

### 2.1. Biopotentials

In previous studies, an abnormal autonomic function was found among fatigued MS patients (Keselbrener *et al* 2000, Flachenecker *et al* 2002); hence, continuous monitoring of the heart condition is considered to be relevant to this study. Therefore, we have developed a 3-lead ECG measurement with two electrodes positioned on the thorax sides and a ground electrode on the right shank. The upper two electrodes are used to detect the cardiac electric activity, while the ground contact electrode is used for the driven-right-leg system (Neuman 2010). An



**Figure 1.** Prototype of the fatigue monitoring system (FAMOS) and the positions of the sensors. ECG: electrocardiograph; EMG: electromyograph.

INA321 CMOS instrumentation amplifier (Texas Instruments, Dallas, TX) is employed as an ECG amplifier, which is single-supply and has a high common mode rejection ratio of 94 dB. A low-pass filter with a cut-off frequency of 100 Hz is integrated in the circuit to suppress the high frequency (HF) noise of the amplified signal and to serve as anti-aliasing filter. The sampling frequency was set at 250 Hz for all data acquisitions.

MS patients frequently complain about weak or painful legs. Many studies have reported that MS patients have lower muscle strength than healthy subjects (Rice *et al* 1992, Kent-Braun *et al* 1997, Dalgas *et al* 2010). It is therefore interesting to monitor the condition of the quadriceps muscles in MS patients over time. In this context, activity and myoelectric fatigue are relevant muscle parameters that can be monitored by EMG. Extensive literature reports on methods and algorithms for the assessment of EMG activity and myoelectric fatigue (Merletti and Parker 2005, Mischi *et al* 2012). We have developed a 3-lead surface EMG measurement with two differential EMG electrodes for continuous monitoring of the muscle activity and a ground electrode for the driven-right-leg system. Two EMG electrodes are positioned between the quadriceps belly and the tendon, avoiding coverage of the innervation point.

Considering the similarity of ECG and EMG amplifiers, we integrated two amplifiers in one circuit, where both ECG and EMG measurements share the same driven-right-leg system. As shown in figure 1, the electrodes are connected to the amplifiers via a DE-9 connector. Compared with the first prototype (Yu *et al* 2010), the new design has smaller size, 30% less weight and less electrodes in use, which improves its utilization. All the adopted electrodes are contact Ag–AgCl electrodes.

## 2.2. Body-skin temperature

Body temperature is also an important physiological parameter, which is controlled by the autonomous nervous system. Vetrugno *et al* (2007) studied the association of fatigue with sleep–wake and body core temperature circadian rhythms among six fatigued patients with MS. No correlation between fatigue and abnormal body core temperature was found. Since it was a small patient group and there was no comparison with controls, we still consider body temperature as a relevant parameter. Body temperature is traditionally measured in the rectum, where the temperature is close to the core temperature, but it is very unpleasant for individuals. Alternative positions that are often used, such as ear, mouth and armpit, are also unsuitable for continuous monitoring. Therefore, we monitored the body temperature by placing a temperature sensor on the skin of the back, as shown in figure 1.

The LM35 is a low cost, linear and low self-heating thermistor. The supply voltage ranges from 4 to 30 V while draining less than 60  $\mu$ A of current. A series R-C damper is added from output to ground for improving the tolerance of capacitance. Since the output signal ranges from 0 to 1 V, it is connected to the NI device directly for data acquisition without amplification.

## 2.3. Motion

It has been reported that fatigued MS patients have reduced physical activity compared with healthy controls (Ng and Kent-Braun 1997, Vercoulen *et al* 1997, Morris *et al* 2002, Motl *et al* 2005). Motion signal is therefore considered as an important functional parameter in this study. Motion signals represent not only the motion state of the subject, but also provide valuable information for robust and accurate analysis of other parameters. It enables, for instance, the precise assessment of starting and ending time of physical activities, supporting the analysis of other physiological parameters.

There were several studies about motion detection with 2-axis or 3-axis accelerometers used as motion sensors (Kawahara *et al* 2007, Jeong *et al* 2007). Normally, the use of a 3-axis accelerometer combined with a gyroscope and a magnetic sensor can provide the possibility for precise motion detection (Zhu and Zhou 2004). However, it requires multiple channels for data acquisition and more space for data storage. It also affects power consumption, reducing battery lifetime. Therefore, we employed two single-axis accelerometers as motion sensors, which cannot provide precise information, but can be used to estimate the motion states of the subject. We chose a MMA1260EG low *g* accelerometer (Freescale, Austin, TX), which has integrated signal conditioning and linear output. The output signal is transferred to the NI device for data acquisition. As depicted in figure 1, motion sensors are placed on the back of each ankle, monitoring the motion of each foot individually.

### 3. Study protocol

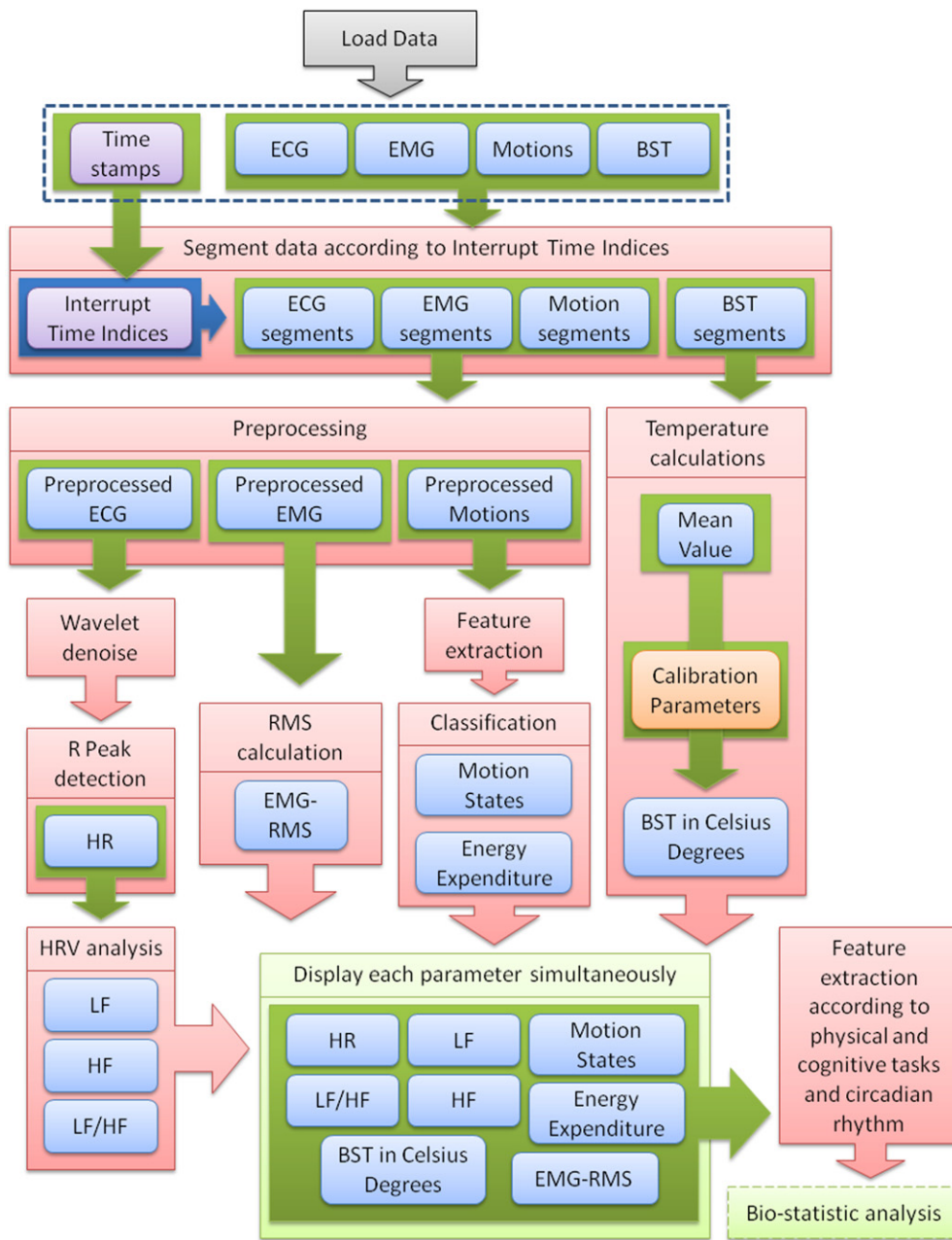
The FAMOS was used in a pilot study to test its ability to distinguish fatigued MS patients from healthy subjects. A total of 26 subjects participated in this study where physiological and functional parameters were recorded for 24 h in the participants' normal daily settings, e.g. at work or at home. Seventeen MS patients were recruited according to the inclusion criteria: (a) definite MS according to the McDonald criteria (McDonald *et al* 2001), (b) mobility (expanded disability status scale (EDSS) score <5.5 (Kurtzke 1983)), (c) definite fatigue according to the fatigue severity scale (FSS) (Krupp *et al* 1989) and (d) age of 20–65. In order to avoid confusion due to secondary fatigue contributors, patients who suffered from depression, severe pain, taking medication that may induce fatigue or being severely cognitively handicapped were excluded from the study. All patients had no known cardiovascular disorders, pulmonary disorders, blood disorders, infections or other disorders except for MS. Additionally, nine age- and sex-matched healthy controls were recruited from the same region. During the monitoring period, the healthy subjects did not suffer from any disease. No difference in demographic data was found between the two groups. The average FSS scores for patient group and control group were 52.3 and 27.25, respectively.

A range of cognitive and functional tests was employed and performed at the beginning of the monitoring period by all the participants. In order to avoid the result being affected by the functional tests due to, e.g., tiredness, a short term memory test (*The memory game* 2009) was completed first. It was followed by 5-repetition of sit-to-stand test, which has been validated and proven reliable in MS patients (Moeller *et al* 2012). After this, a walk test (Collen *et al* 1990) at both usual and fastest speeds was completed. To conclude, 50-repetition of sit-to-stand test were performed to induce physical stress in the subjects.

### 4. Data analysis

A software package to analyse FAMOS recordings was developed in LabVIEW (NI, Austin, TX). Figure 2 depicts the overview of the processing algorithms and data flow for ECG, EMG, BST and motion activity signals. The data of each parameter and time stamps are first loaded. According to the interrupt time indices, each signal is separated into several segments. ECG, EMG and motion signals pass through a preprocessing procedure, which involves a high-pass, a notch and a low-pass filter, prior to the dedicated feature extraction algorithms. The root mean square (RMS) of the EMG is calculated. Based on motion signals, we obtained the motion states and an estimated energy expenditure across the whole monitoring period. In





**Figure 2.** Overview of the processing algorithms and data flow for estimation of multiple physiological and functional parameters. ECG: electrocardiograph; EMG: electromyograph; BST: body skin temperature; HR: heart rate; RMS: root mean square; HRV: heart rate variability; LF: low frequency components of HRV; HF: high frequency components of HRV; LF/HF: LF to HF ratio.

addition, the body-skin temperature signal is converted into Celsius degrees and is displayed together with the other features in a list of graphs.

We extracted a number of features from the measured signals during the cognitive test and the functional tests, and during the whole monitoring period. The heart rate variability (HRV)

during each task and during the rest phase after the tasks were considered as important features. The low frequency (LF) components, the HF components and the LF/HF ratio according to the defined frequency bands (Montano *et al* 1994) were calculated. The mean value and standard deviation of heart rate, RMS of the EMG signal and average BST during the tests and rest phases were extracted. The ratios of overall active time  $R_{OA}$  and overall energy expenditure  $R_{EE}$  were also calculated. The algorithms implemented for feature extraction are described as follows for each separate signal.

#### 4.1. Data segment selection

During the monitoring process, there were interrupts due to system errors of wireless communication. For example, a subject was moving out of the wireless signal range. Gaps in the continuous data have to be detected before implementing any processing algorithms. Thus, the first processing procedure is to detect the interrupted time stamps and, based on the detection, separate the signal into segments.

Clock time stamps were continuously recorded every 2 s along with the measured signals. Following a three-step calculation based on the clock time stamps, we can find the interrupted time stamps. To this end,

- we first convert the clock time stamps to seconds;
- then measure the intervals between the adjacent time stamps by subtracting each stamp from the previous one;
- those with an interval larger than 10 s are considered as interrupted time stamps, i.e. there must be a gap such that no signal was recorded in this time interval.

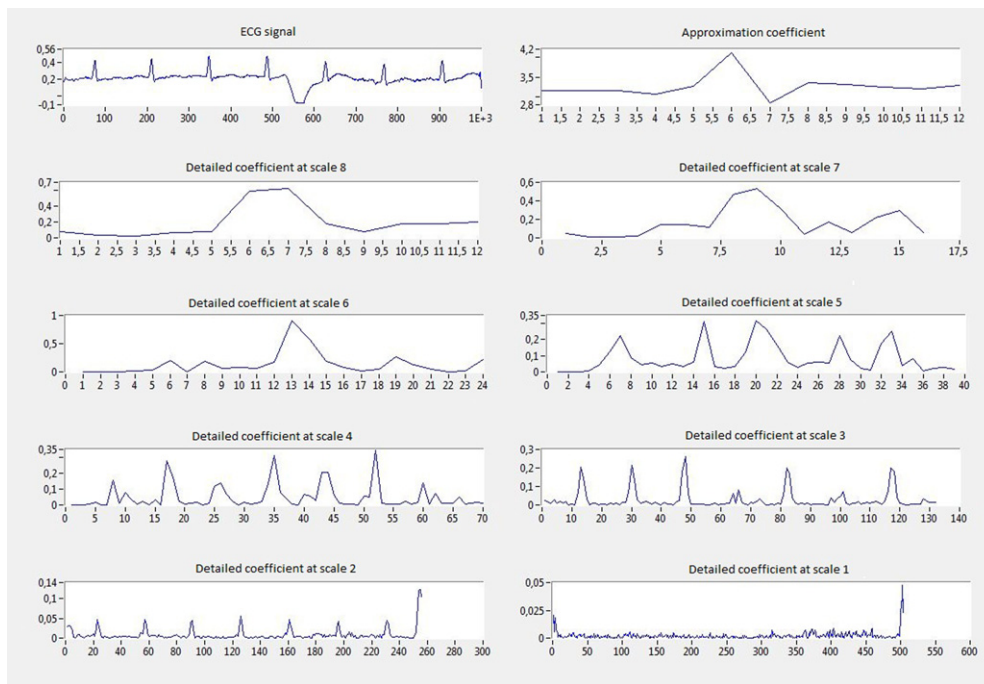
According to the detected interrupt time stamps, we can search for the interrupt indices from the time stamp array. Because the indices of the time stamp are correlated with the indices of the signals, we can then separate the signals based on the interrupt indices.

#### 4.2. Electrocardiography implementation strategy

**4.2.1. Preprocessing.** ECG recordings are typically affected by baseline wander, power line and higher frequency noise. Preprocessing by proper filtering is therefore required (Kohler *et al* 2002). A second-order Butterworth filter is employed in the design of all the IIR filters. First, the baseline wander is removed by a high-pass filter with cut-off frequency at 0.01 Hz. As IIR filters cause nonlinear phase distortion, the signal is inverted and filtered a second time to compensate for the phase distortion. This is adopted for all the IIR filters. A notch filter at 50 Hz is used to suppress the power line interference. A low-pass filter with a cut-off frequency of 100 Hz is then used to suppress HF noise.

**4.2.2. Wavelet denoising.** In order to improve robustness to noise and artefacts, wavelet denoising is used prior to R-peak detection. Several mother wavelets have been used in previous studies on heart rate variability analysis (Li *et al* 1995, Thurner *et al* 1998, Mahmoodabadi *et al* 2005, Zhang 2005). We selected Symlet-5 as a mother wavelet, which is orthogonal with five vanishing moments and has close similarity to the QRS complex.

From the preprocessed signal, eight scales are computed. As depicted in figure 3, the transformed signal comprises nine segments including the largest scale of the approximation coefficient and eight scales of the detailed coefficients. The first graph shows the preprocessed ECG signal which has an artefact from 500 to 600. The approximation coefficient, computed by the scaling function as a low-pass filter, contains the spectrum of baseline wander. Detail



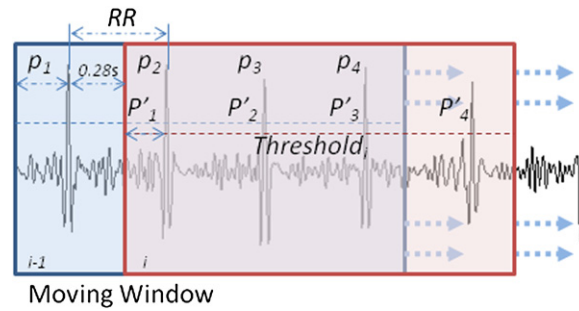
**Figure 3.** Eight scales discrete wavelet transform of an ECG signal using mother wavelet Symlet-5.

coefficients at scales 8 and 5 represent the artefact as the main components, while at scale 1, it does not represent much of the R-peaks. At scale 2, there is a good representation of the R-peaks, but it has influence from the edges. Therefore, we select the detailed coefficients at scales 3 and 4, which contain most of the R-peak energy. Different from other algorithms, in which R-peaks were directly detected from the selected scales, we reconstruct the signal using the inverse wavelet transform at the selected scales. Then we compute the cross correlation with a clear R-wave pattern, selected from the preprocessed signal, to enhance the R-wave components. Due to the nature of the portable measurement system, this is an important step for reliable R-peak detection.

**4.2.3. R-peak detection.** Rooijackers *et al* (2012) recently developed a low complexity R-peak detection algorithm for ambulatory fetal monitoring, in which a dynamic threshold was employed to detect the R-peak in a moving window. In our study, a fixed length window of 2 s is employed for R-peak detection, which moves according to the detected R-peak position. Within each window,  $i$ , a threshold,  $Th_i$ , is set based on the average amplitude of the previous detected R-peaks, i.e.

$$Th_i = \frac{c}{n} \sum_{k=1}^n A_{i-1}(k), \quad (1)$$

where  $A_{i-1}(k)$  is the amplitude of the  $k$ th R-peak in the previous windows  $i - 1$ ,  $n$  is the number of detected R-peaks and  $c$  is a tunable parameter. If more than one peak is detected within 200 ms, then the one with the maximum amplitude is considered as the true R-peak. In each window, we only use the first valid R-peak for further calculations, e.g., heart rate and



**Figure 4.** Moving window for R-peak detection.

next position of the moving window. Assuming the shortest RR interval to be at least 0.28 s long, the next window starts 0.28 s after the first peak, and the RR interval is given as

$$RR = P_1 + 0.28, \quad (2)$$

where RR is the length of RR interval expressed in seconds and  $P_1$  is the first R-peak position in the current window, i.e. the interval from the peak to the left edge of the window. Figure 4 illustrates the R-peak detection process. In the first moving window  $i - 1$ , the  $Th_{i-1}$  detects four R-peaks, in which the average of the amplitudes determine the new  $Th_i$ .  $P_1$  is chosen to calculate the starting position of the next window  $i$  by adding 0.28 s. Again, the amplitudes of the detected R-peaks in window  $i$  determine the next  $Th_{i+1}$ , and the first R-peak position  $P'_1$  is selected for further calculations. The RR interval is equal to  $P'_1 + 0.28$ . This process is repeated until all the R-peaks are detected.

**4.2.4. Heart rate variability.** HRV is typically assessed by the spectral analysis of the LF and HF bands of the RR interval. The LF and HF components, which are defined from 0.04 to 0.15 Hz and from 0.4 to 1.5 Hz, occur in synchrony during vasomotor and respiratory acts, respectively (Montano *et al* 1994). The power of such components reflects their reciprocal relationship. The LF/HF ratio is used as an index of sympathovagal balance (Montano *et al* 1994). The LF component, the HF component and the LF/HF ratio are therefore calculated for further analysis.

### 4.3. Electromyography

Similar to the ECG signal processing algorithm, the raw EMG signal is preprocessed by the same high-pass filter and notch filter, and by a low-pass filter with a cut-off frequency of 125 Hz. Muscle activity can be measured by the RMS value of the EMG signal, which can be calculated as the square root of the average power for a given time window (Merletti and Parker 2005). A moving window with a length of 4 s and moving step of 0.5 s is employed to estimate the RMS.

### 4.4. Thermometry

The LM35 precision centigrade temperature sensor has linear output voltage proportional to temperature. Since body-skin temperature changes slowly, we compute the mean value for 1 s of signal. The output signal is then fitted with the linear model:

$$T = c_1x + c_2, \quad (3)$$

where  $T$  and  $x$  are temperature in °C and output voltage, respectively. The slope  $c_1$  and the intercept  $c_2$  are the parameters obtained from the Calibration. ATC-156A from METEK Calibration Instruments was used to calibrate the temperature sensor. A range of 21 °C from 25 to 45 °C with 1 °C interval was used for calibration. Equation (3) was fitted to the recorded data by a least-squares method to derive the slope  $c_1$  and the intercept  $c_2$ .

To suppress artefacts, we implement a denoising procedure as follows. Firstly, compute the average temperature in the previous 10 s  $Ta_i$ . If the current temperature  $T_i$  changes significantly with  $|T_i - Ta_i| \geq 1^\circ\text{C}$ , then  $T_i$  is considered as an artefact and is replaced by  $Ta_i$ .

#### 4.5. Motion detection strategy

A moving window with 1 s length and 0.5 s moving step is employed to process the accelerometer-captured signals. A signal pace segment, which was recorded during the walk test, is saved as a reference pattern to enhance the signal during walking by cross correlation. We compute the standard deviation of the preprocessed signal to discriminate between the static state (no motion) and motion. Two thresholds, which were selected with the best accuracy according to receiver operating characteristic curve (Brown and Davis 2006), are applied on the obtained two signals that enabled the classification of the motion states as either static, walking or other motion.

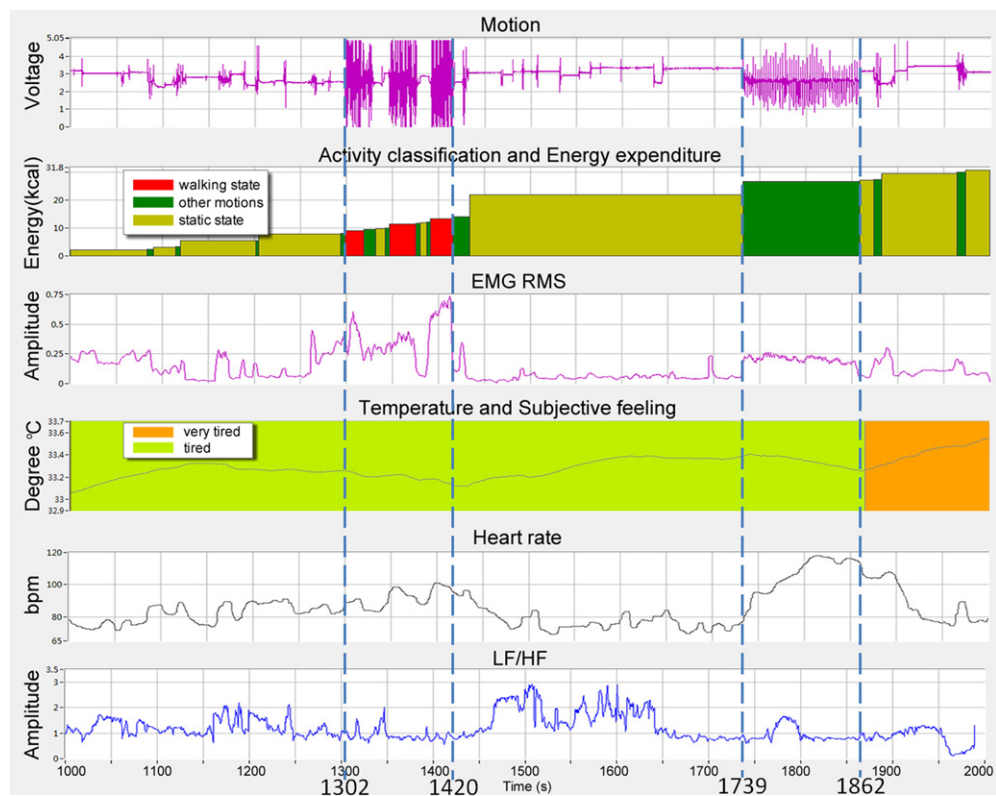
According to the classified motion states, we estimate the daily physical activity of each participant, including the overall time of non-static motion states and the overall energy expenditure. The latter parameter is calculated following the energy expenditure equation (Ryu *et al* 2008), defined by the American College of Sports Medicine. Because the total testing time differed among participants, we normalize these two parameters with respect to the total testing time.

## 5. Results

All the estimated parameters are displayed simultaneously according to the same time axes. Figure 5 illustrates an example with several plotted parameters. The first plot shows the accelerometric signal, from which both motion states and energy expenditure are extracted. The second plot presents these two features. According to the diary, which was reported by the subject, the phase of ‘walking state’ from 1302 to 1420 s and the phase of ‘other motion state’ from 1739 to 1862 s are related to the walk test and 50-repetition sit-to-stand test, respectively. The ‘static state’ between these two phases is therefore a rest phase. The EMG–RMS is correlated with the motion states. As shown in the third graph, the amplitudes of the estimated parameters during walking and other motion phases are higher than the amplitudes during static state. The heart rate, shown in the fifth plot, increased during the physical tasks, especially during the 50-repetition sit-to-stand test, resulted in significantly higher heart rate than during the rest phase. Besides, the subjective feelings, which were indicated by the participant, are illustrated in the fourth plot together with the temperature estimates.

One-way ANOVA is used in the pilot study for statistical analysis of the estimated parameters in different groups. The significance was set to  $p < 0.05$ . Table 1 lists the most relevant results of the pilot study. The data marked with ‘\*’ indicate a significant difference between patient group and control group.

Patients performed more poorly than controls on both the cognitive and physical tests, and they were less active and had less energy expenditure during the whole monitoring process. The standard deviation of the heart rate in patients during the memory test is significantly lower than in controls. During rest following the walk test, the HF component in MS patients



**Figure 5.** Plots of multiple parameters from the pilot study.

is also significantly lower compared to controls. MS patients have significantly higher LF/HF ratio during the 50-time sit-to-stand test. Moreover, BST in MS patients also varied more than in healthy controls. The physiological parameters during the walk test are not different between the two groups. Other parameters, which are not listed in table 1, such as the mean heart rate, RMS-EMG and mean temperature, do not show a significant difference during either the physical or the cognitive tests.

## 6. Discussion

fMRI studies have succeeded in finding evidence of association between several defined anatomical brain areas and fatigue in MS. However, due to the limitations of such measurements, it is not clear whether additional mechanisms relate to fatigue. Based on current technology, devising portable brain imaging equipment, i.e. a wearable MRI, is still infeasible. Therefore, until now, fatigue has only been assessed by questionnaires in clinical settings.

The FAMOS enables continuous monitoring of multiple physiological and functional parameters, as well as the feeling of fatigue. The subjective feeling and objective parameters are displayed simultaneously. It provides a tool for analysing each parameter in relation to fatigue in MS. According to the pilot study, in which 26 participants were monitored continuously without interfering in their normal daily routines, the FAMOS evidences significant differences

**Table 1.** The preliminary results of the pilot study. All the parameters are presented with mean  $\pm$  standard deviation.

Phase of interest	Parameters	MS patients	Controls
During the memory test	SD <sub>HR</sub>	2.81 $\pm$ 0.91*	4.95 $\pm$ 1.48*
	LF	2741 $\pm$ 1169*	4461 $\pm$ 2076*
	HF	1546 $\pm$ 625*	2508 $\pm$ 871*
	LF/HF	1.79 $\pm$ 0.38	1.74 $\pm$ 0.53
	SD <sub>BST</sub>	0.10 $\pm$ 0.10	0.11 $\pm$ 0.06
	Test result	7 $\pm$ 3*	11 $\pm$ 2*
During the walk test	SD <sub>HR</sub>	8.2 $\pm$ 6.5	7.4 $\pm$ 6.4
	LF	408 $\pm$ 397	243 $\pm$ 322
	HF	477 $\pm$ 450	378 $\pm$ 359
	LF/HF	0.77 $\pm$ 0.52	0.47 $\pm$ 0.35
	SD <sub>BST</sub>	0.10 $\pm$ 0.15	0.03 $\pm$ 0.04
	Walk speed	1.1 $\pm$ 0.3*	1.6 $\pm$ 0.2*
During rest following the walk test	SD <sub>HR</sub>	4.7 $\pm$ 3.5	5.3 $\pm$ 3.0
	LF	194 $\pm$ 104	423 $\pm$ 343
	HF*	294 $\pm$ 170	643 $\pm$ 450
	LF/HF	0.74 $\pm$ 0.28	0.82 $\pm$ 0.51
	SD <sub>BST</sub>	0.38 $\pm$ 1.07	0.07 $\pm$ 0.15
	SD <sub>HR</sub>	12.5 $\pm$ 3.8	12.6 $\pm$ 2.9
During the 50-repetition sit-to-stand test	LF	3574 $\pm$ 1499	2686 $\pm$ 1250
	HF	3924 $\pm$ 1654	3455 $\pm$ 1433
	LF/HF	0.91 $\pm$ 0.05 <sup>a</sup>	0.75 $\pm$ 0.09 <sup>a</sup>
	SD <sub>BST</sub>	0.31 $\pm$ 0.22 <sup>a</sup>	0.04 $\pm$ 0.02 <sup>a</sup>
	Test speed	139.2 $\pm$ 34.4 <sup>a</sup>	95.6 $\pm$ 22.9 <sup>a</sup>
During the whole monitoring period	R <sub>OA</sub>	0.28 $\pm$ 0.23 <sup>a</sup>	0.53 $\pm$ 0.29 <sup>a</sup>
	R <sub>EE</sub>	109 $\pm$ 12 <sup>a</sup>	122 $\pm$ 15 <sup>a</sup>

SD<sub>HR</sub> is the standard deviation of heart rate. LF, HF and LF/HF represent the LF component, the HF component and the LF/HF ratio, respectively. SD<sub>BST</sub> is standard deviation of BST. R<sub>OA</sub> and R<sub>EE</sub> are the ratio of the overall active time and overall energy expenditure, respectively.

<sup>a</sup> Indicates significant difference between the two groups with  $p < 0.05$ .

between fatigued MS patients and healthy controls. Motion features may be considered as indirect indices of fatigue. Both the motion estimates during the whole monitoring period and the physical-test results indicate reduced physical activity in fatigued MS patients. In addition, the LF-to-HF ratio in patients is significantly higher than in controls during the 50-repetition sit-to-stand test, indicating disturbed sympathovagal balance, where parasympathetic nerves are dominating. The abnormal body-skin temperature pattern also suggests a certain degree of autonomic dysfunction in fatigued MS patients. These findings indicate that when fatigued MS patients are exposed to both cognitive and physical tests, they have a different autonomic response compared to healthy controls. These results from the pilot study confirm the ability of the FAMOS to distinguish fatigued MS patients from healthy control subjects.

The FAMOS also shows some limitations. The system, for instance, is limited to indoor utilization due to wi-fi signal range. An improved method making use of local data storage and intelligent wireless communication strategy will improve the utilization to outdoors. Considering the goal of this study is to test whether fatigued MS patients can be distinguished from healthy controls by using a wireless wearable measurement system, we realized a simple

hardware solution. Size and weight of the hardware, communication module of sensors and power consumption of the system can be further improved. In addition, the usability and reliability of the FAMOS should be further improved and validated through larger clinical trials. After that, a classifier, e.g., based on machine learning, could be implemented and trained with larger datasets to process the measured set of parameters.

## 7. Conclusion

This paper presents the realization of a wireless measurement system. Both hardware design and implementation of dedicated signal processing are reported. In this pilot study, the FAMOS performed continuous data acquisition and extraction of multiple physiological and functional parameters, which can be used to distinguish fatigued MS patients from healthy controls. Compared with other MS studies, the pilot study was the first study monitoring multiple physiological and functional parameters continuously in a normal daily setting. Several cognitive and physical tests were involved during monitoring, and numerous features can be extracted from our data. Therefore, we conclude that the FAMOS provides a new and flexible objective approach to study fatigue in MS. Since the measured data contain continuous information on physiological parameters and functions, several features can be extracted for different medical studies. The use of the FAMOS is, thus, not necessarily limited to study fatigue in MS.

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