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Relationship between physical activity and central sensitization in chronic low back pain: Insights from machine learning

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ABSTRACT

Background and objectives: Chronic low back pain (CLBP) is a leading cause of disability. The management guidelines for the management of CLBP often recommend optimizing physical activity (PA). Among a subsample of patients with CLBP, central sensitization (CS) is present. However, knowledge about the association between PA intensity patterns, CLBP, and CS is limited. The objective PA computed by conventional approaches (e.g. cut-points) may not be sensitive enough to explore this association. This study aimed to investigate PA intensity patterns in patients with CLBP and low or high CS (CLBP-, CLBP+, respectively) by using advanced unsupervised machine learning approach, Hidden semi-Markov model (HSMM).

Methods: Forty-two patients were included (23 CLBP-, 19 CLBP+). CS-related symptoms (e.g. fatigue, sensitivity to light, psychological features) were assessed by a CS Inventory. Patients wore a standard 3D-accelerometer for one week and PA was recorded. The conventional cut-points approach was used to compute the time accumulation and distribution of PA intensity levels in a day. For the two groups, two HSMMs were developed to measure the temporal organization of and transition between hidden states (PA intensity levels), based on the accelerometer vector magnitude.

Results: Based on the conventional cut-points approach, no significant differences were found between CLBP- and CLBP+ groups ($p = 0.87$). In contrast, HSMMs revealed significant differences between the two groups. For the 5 identified hidden states (rest, sedentary, light PA, light locomotion, and moderate-vigorous PA), the CLBP- group had a higher transition probability from rest, light PA, and moderate-vigorous PA states to the sedentary state ($p < 0.001$). In addition, the CBLP- group had a significantly shorter bout duration of the sedentary state ($p < 0.001$). The CLBP+ group exhibited longer durations of active ($p < 0.001$) and inactive states ($p = 0.037$) and had higher transition probabilities between active states ($p < 0.001$).

Conclusions: HSMM discloses the temporal organization and transitions of PA intensity levels based on accelerometer data, yielding valuable and detailed clinical information. The results imply that patients with CLBP- and CLBP+ have different PA intensity patterns. CLBP+ patients may adopt the distress-endurance response pattern with a prolonged bout duration of activity engagement.

1. Introduction

Chronic low back pain (CLBP) is a globally prevalent chronic musculoskeletal disorder [1] and is costly due to medical treatments and work productivity loss [2]. Additionally, it is a leading cause of high levels of disability [3]. In the management of CLBP, optimizing physical activity (PA) is often recommended [4]. However, the results of studies that examine PA intensity levels between patients with CLBP and healthy controls are inconsistent. Some studies suggest that people with CLBP exhibit lower overall PA intensity levels (averaged over one day or several days), com-

Abbreviations: CLBP, chronic low back pain; PA, physical activity; CS, central sensitization; CLBP+, chronic low back pain with higher central sensitization levels; CLBP-, chronic low back pain with lower central sensitization levels; HSMM, hidden semi-Markov model; AEM, avoidance-endurance model; CSI, central sensitization inventory; VAS, visual analogue scale; PDI, pain disability index; Rand36-PF, physical functioning subscale of the Rand36; PCS, pain catastrophizing scale; IEQ, injustice experience questionnaire; BSI, brief symptom inventory; BIC, bayesian information criterion; JSD, Jensen–Shannon divergence; MET, metabolic equivalent of Task; mg, milli-gravity; DE, distress-endure.

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pared to matched controls [5,6], while others have reported that overall PA intensity levels do not differ significantly between patients with CLBP and healthy controls [7,8]. With respect to the PA distribution during a day, one study reports that CLBP patients have significantly lower overall PA intensity levels in the morning compared to healthy controls [8] while another study observes that during the evening, CLBP patients are significantly less active than healthy controls [9].

One explanation for the inconsistencies might be the heterogeneity within the population of CLBP. A subsample of patients with CLBP might have central sensitization (CS) [10]. CS is the increased responsiveness to noxious and non-noxious stimuli [11]. A recent paper proposes two major sub-types of CS: a "bottom-up" type and a “top-down” type [12]. The “bottom-up” type may be driven by persistent peripheral noxious input, causing an imbalance in excitatory and inhibitory central neurotransmitters, and altering gene regulations in the central nervous system, leading to central hyperexcitability. The “top-down” type is suggested to be driven without ongoing nociceptive input and the primary contribution may originate in supraspinal structures, including the psychosocial symptoms, such as fear-avoidance beliefs and pain catastrophizing thoughts. These symptoms may enhance forebrain activity, i.e. the neuronal activation of the prefrontal cortex and the limbic system, leading to central hyperexcitability. Central hypersensitivity eventually can spread and expand to multiple brain regions [12]. Consequently, patients with CS may be present with widespread hyperalgesia, fear-avoidance beliefs, pain catastrophizing thoughts, anxiety, and depression [12] The relation between CS and PA is still unclear but the plausibility of this relation can be derived from relations between fear-avoidance beliefs, pain catastrophizing thoughts, and pain levels on the one hand and CS on the other [13]. Both the fear-avoidance model [14] and the avoidance-endurance model (AEM) [15] postulated that fear beliefs and catastrophizing thoughts could eventually lead to physical inactivity and lower PA intensity levels [16]. However, the evidence on the relation between fear beliefs and measured PA is inconsistent [17–19]. To evaluate the relationship between AEM and PA in CLBP, one study compares the PA (measured by accelerometer) between avoiders and persisters (labeled by Patterns of Activity Measure-Pain questionnaire), but the results do not show differences between these 2 groups [17]. This finding is supported by another study which reports that, among a CLBP sample, none of the objective measures of PA were associated with fear beliefs and this finding does not support one aspect of the fear-avoidance model that fear beliefs are associated with physical inactivity [18]. This might be due to the fact that PA intensity is studied in terms of average intensity levels over for instance days, which lacks sensitivity to detect small differences, since a recent study reports that fear beliefs and catastrophizing are associated with the distribution of PA at a day instead of the average PA levels [19].

Therefore, to obtain more in-depth knowledge about the impact of CLBP and CS levels on PA, the temporal organization (distribution) as well as the transitions between PA intensity levels provide important information. For instance, with the same accumulated time of sedentary activity, it makes a difference if someone takes regular small bouts of activity in-between sedentary times or not. Small bouts of activity can counteract the harmful effects of a prolonged sedentary period [20]. Similar, frequent short bursts of moderate-vigorous PA may have smaller health benefits than less frequent but longer periods of moderate-vigorous PA [21]. Knowing the differences in the PA intensity patterns of patients with CLBP and low or high CS will provide us with knowledge regarding the possible underlying mechanism of CLBP and assist in the development of personalized rehabilitation programs.

The well-established approach to study PA intensity levels is the cut-points approach which is based on predefined acceleration thresholds (e.g. activity counts/per minutes) to divide the acceleration data into sedentary (<100), light (100–1951), and moderate to vigorous (>1951) PA intensity levels based on healthy populations [22]. By using the predefined thresholds, this approach provides a standardized method for classifying PA intensity levels, allowing for comparability across studies. However, predefined thresholds for PA intensity levels are most often based on healthy populations which may not accurately reflect small changes in PA intensity levels of patient populations. For instance, PA levels of patients with lumbar spinal stenosis disease are all identified as sedentary and light, despite small changes in PA intensity having significant clinical implications [23]. Furthermore, the thresholds may vary with age, and may not provide an accurate and precise PA intensity level assessment for every individual. To get more accurate PA intensity levels, supervised machine learning approaches [24], such as Naive Bayes, K-nearest neighbors [25], random forest [26], support vector machines [27], and artificial neural network [28], are used to classify the PA intensity levels or predict the continued metabolic equivalent of task (MET) values based on the labeled accelerometer data. Although supervised machine learning approaches show potential for accurate PA intensity assessment, but require labeled data that are labeled with different PA intensity levels or METs prior to the model training. To get rid of the need of a-priori information (predefined thresholds or labeled data), unsupervised machine learning approaches (such as K-means [29], density-based spatial clustering of applications with noise [30], and hierarchical clustering [29]) are used to cluster the PA intensity levels from accelerometer data. However, the outcomes of the above approaches are usually used to compute average or summary statistics from one- or several-time windows instead of providing more in-depth information about the temporal organization and transitions between PA intensity levels. Hidden semi-Markov model (HSMM) [31] is considered as an unsupervised machine learning approach as well as a probabilistic graphical model [32]. The characteristic of the probabilistic graphical model enables HSMM to disclose the temporal organization and transition information of PA intensity levels. Therefore, HSMM has several advantages. First, it is a data-driven approach. It can get rid of resources expensive calibration or data labeling. Second, HSMM has higher resolution by clustering PA intensity levels (hidden states) from acceleration than the cut-points approach, instead of 4 levels of intensity (sedentary, light, moderate, and vigorous PA). Third, more in-depth information, such as temporal organization and transitions of PA intensity levels may provide a more parsimonious and biologically informative description of the data. Fourth, differences in temporal organization of and transitions between PA intensity levels from HSMM between groups can be statistically tested, and therefore, differences between groups may be recognized.

This study aimed to investigate whether low or high CS levels are associated with different PA intensity patterns (temporal organization of and the transitions between PA intensity levels) of patients with CLBP, using HSMM (based on daily-living accelerometer data). The highlights and contributions of this paper can be summarized as follows:

- The paper shows that the applicability of HSMM provides detailed and valuable clinical information about temporal organization and transitions of PA intensity levels based on accelerometer data.
- The analytic strategy used in this study provides a deeper understanding of the relationship between PA, CS, and CLBP.
- A comparison of the HSMM results with the conventional cut-points approach showed that the cut-points approach did not find statistical differences in patients with high or low levels of CS while HSMM did.

- Different PA intensity and transition patterns between patients with high levels and low levels of CS were found, implying the need for different intervention strategies

2. Material and methods

2.1. Patients

Patients aged between 18 and 65 years old who had primary CLBP were recruited from the outpatient Pain Rehabilitation Department of the Center for Rehabilitation of the University Medical Center Groningen (CvR-UMCG). Primary CLBP is defined as low back pain persistent for more than three months, with pain not being the result of any other diagnosis [33]. Criteria for excluding patients from these studies were: (a) had a specific diagnosis that would better account for the symptoms (e.g. cancer, inflammatory diseases and/or spinal fractures); (b) had neuralgia and/or radicular pain in the legs; (c) were pregnant.

The study was approved by the Medical Research Ethics Committee of the University Medical Center Groningen (METc 2016/702). Informed consent was obtained from all subjects and this study was conducted according to the principles expressed in the Declaration of Helsinki. The data used in this paper were derived from a larger study, in which protocol details were described elsewhere [34]. From the same sample, a study about gait analysis was published [35].

2.2. Data collection

2.2.1. Central sensitization (CS)

The presence of CS-related manifestations was assessed with section A of the Central Sensitization Inventory (CSI) [36]. Section A has 25-items to assess the presence of common CS-related symptoms. Scores can range from 0 to 100 where a higher score represents a higher level of CS. A score lower than 40 indicates low CS (CLBP- group) and a score of 40–100 indicates moderate-high CS (CLBP+ group) [37].

2.2.2. Secondary measures

Clinical data were measured via self-reported questionnaires. The Visual Analogue Scale assesses the pain intensity (VAS Pain; 0–10). VAS scores lower than 3.4 represent mild pain, between 3.5 to 7.4 represent moderate pain, and higher than 7.5 represent severe pain [38]. The Pain Disability Index (PDI; 0–70) with higher scores reflect higher interference of pain with daily activities. The physical functioning subscale of the Rand36 questionnaire (Rand36-PF; 0–100) with higher scores represent lesser disability. The Pain Catastrophizing Scale (PCS, 0–52), the Injustice Experience Questionnaire (IEQ, 0–48), and the Brief Symptom Inventory (BSI global severity index t-score) were used to assess psychological-related symptoms. The PCS scores [39] and IEQ scores [40] over 30 are associated with clinical relevance, and higher scores of BSI relate to more severe psychological symptoms.

2.2.3. Accelerometer data collection and formating

Patients were instructed to wear a tri-axial accelerometer (ActiGraph GT3X, Actigraph Corporation, Pensacola, FL) at all times for about one week, excluding sleeping or bathing time. The accelerometer was worn at the front right hip of the patient (at the anterior superior iliac spine). The sampling frequency of the accelerometer was set to 100 Hz and the dynamic range was ± 6 gravity.

The raw data of each patient was firstly segmented into 24-h span data segments (from 12:00 PM. to the next day 11:59 A.M). This time span was used because the measurement started at 12:00 PM. Secondly, the data that did not completely cover this 24 h span was discarded. For technical or patient-related reasons, most of the patients did not have a full week of data. In order to compare the data between different patients fairly, 4 segments (representing 4 days) of each patient were randomly selected.

2.3. Conventional cut-points approach

The cut-points approach were set as sedentary (<100 counts/min), light physical activity (100 to 1951 counts/min), and moderate-to-vigorous physical activity (> 1952 counts/min). These thresholds have been reported by a former study [22]. The activity count [41] is an objective index to assess the energy expenditure of activities. It is generated from the accelerometer data following frequency filtering, thresholding, rectification, and integration processing. The accelerometer data was resampled to 30 Hz. Then, a bandpass Butterworth filter with 4 orders was applied. Another filter with coefficient matrices which were found by [41] was used. The filtered data was truncated to 0 if the value was smaller than the threshold of 0.068. Finally, consecutive samples were accumulated into the 5-s epoch counts data. In this study, the activity count was computed based on accelerometer data by using the package ActigraphCounts [42].

2.4. Hidden semi-Markov model

For each 24 h span data segment, the gravity effects were removed from the 3-axis raw accelerometer data (details of this process was in Appendix A) and then computed the vector magnitude as: acceleration $= \sqrt{accX^{\,2} + accY^{\,2} + accZ^{\,2}}$. This vector magnitude was simply called acceleration in this study. Next, the acceleration during unworn time in the night was removed from each segment. The unworn time was defined as the period which acceleration values were all 0 and lasting longer than 3 h. Finally, the acceleration was average across every 5 s. These acceleration segments were used to train HSMMs later.

The acceleration segments of CLBP- and CLBP+ group were separately used to train two HSMMs respectively. HSMM was used to explore the different PA intensity levels from acceleration. It is an unsupervised machine learning approach, and it can automatically cluster hidden states from the observation data (acceleration). Hidden states are not directly observed from the acceleration but are inferred from clusters of the acceleration. HSMM cannot provide the physical meaning of hidden states, but hidden states can be interpreted as PA intensity levels because they were clustered from the acceleration and contained characteristics of acceleration values and duration.

Before training HSMM, the number of hidden states M should be determined. On the one hand, a high number of states may fit the observation data better but will increase the model complexity and overfitting danger. On the other hand, a small number of states is easier to interpret the resulting states and more computationally efficient but may lead to underfitting. So, estimating M is a matter of balancing between model complexity and model performance. The Bayesian Information Criterion (BIC) has been widely used to help model selection and it takes model complexity and model performance into consideration [43]. In this study, BIC was used to help to determine the number of states (More details of BIC are shown in Appendix B).

Let $S = \{s_1, s_2, \ldots, s_M\}$ be a set of hidden states, and $O = \{o_1, o_2, \ldots, o_T\}$ be the set of observations (acceleration). HSMM is defined as $\lambda = (\pi, A, B, C)$:

- π is the initial probability distribution of hidden sates. $\pi = \{\pi_1, \pi_2, \ldots, \pi_M\}$, where $\sum_i \pi_i = 1$.

- A is the hidden states transition matrix and its element is denoted by a_{ij},where $i \neq j$ and $\sum_i a_{ij} = 1$. a_{ij} represents the probability of hidden state s_i transiting to hidden state s_j.
- B is the emission probability matrix. The emission probability of observation data from time a to b, given the current state in s_i is $b_i(o_a^b)$. In this study, emission probability was modeled as Gaussian distributions.
- C is the duration probability matrix and it is represented by $c_i(d)$, where d is the duration of current hidden state s_i, $d \in \{1, 2, \ldots, D\}$. The durations are modelled as discrete Poisson distribution. In order to reduce the training time, the maximum duration D is set to 2 h.

The parameters of HSMM were learned by Bayesian estimation with a Gibbs sampler. The model was trained until the hamming distance between the assigned states of two consecutive iterations was smaller than 0.05. Then, the model was treated as convergent and had a stable parameter set. The implementation of HSMM was based on the package Pyhsmm [44].

After the model training, every acceleration segment has a corresponding hidden state sequence which shows the temporal distribution of PA intensity levels. The hidden state sequences are called fingerprints in this study because they represent the PA intensity distribution of individual patients. In order to show the full 24 h fingerprint of each segment, the unworn time was added to the fingerprint based on the original timestamp. The input and output of the HSMM training process are shown in Fig. 1.

2.5. Statistical analysis

An independent T-test was applied to examine the differences in the overall or day-averaged PA intensity levels between CLBP- and CLBP+ groups. These PA intensity levels were calculated using the cut-point approach.

Significant differences in outcomes between the two HSMMs trained by the acceleration of CLBP- and CLBP+ groups were assessed using independent T-tests (duration and accumulation of time of hidden states) or binomial proportion tests [45] (hidden state transitions) (details of binomial proportion tests are shown in Appendix C).

For all analyses, the p-value was set to 0.05. The Jensen–Shannon divergence (JSD) was used to measure the similarity between the emission probability. Smaller values (minimum 0) indicate more similarity. In this study, all analyses were conducted offline and were performed using the Python.

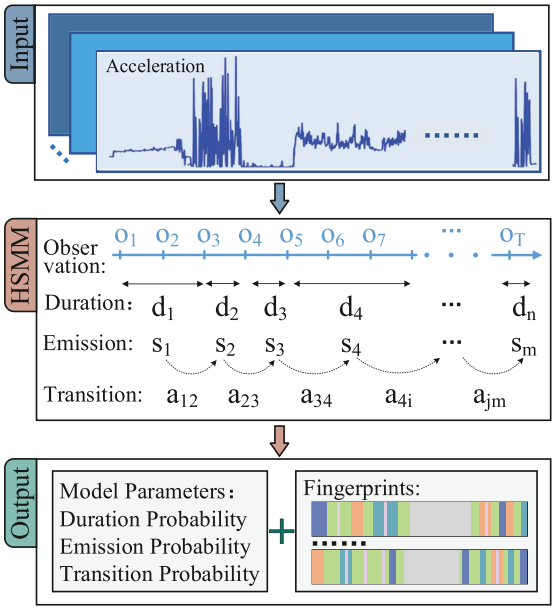

Fig. 1. HSMM training process. Input: the input data of the model; HSMM: hidden semi-Markov model; Output: the output after the model training; O: observation (acceleration) data; d: duration of the observation; s: hidden sate; a: transition probability.

To interpret the physical meaning of hidden states, the walking events were identified from the accelerometer data. Walking is a common activity during the day, and it is reported that the MET value of moderate pace walking (1.25–1.43 m/s) is 3.5 METs [46]. The details of walking event detection, step frequency, and walking speed calculations are shown in Appendix D.

3. Results

3.1. Demographic results

Of the 60 patients, 7 patients were excluded due to lack of measurements for sufficient numbers of days (<4 days) by accelerometry; 11 patients were excluded due to the missing CSI scores. Finally, 42 patients were included in the data analysis. Patients in CLBP- and CLBP+ groups had similar demographic and clinical characteristics, with the exception of CSI score ($p < 0.0001$) and BSI ($p = 0.01$) (see Table 1 for demographics, for a more detailed demographics see [35]). CLBP- and CLBP+ had moderate pain and

Table 1
Patient characteristics ($n = 42$).

	CLBP- ($n = 23$)	CLBP+ ($n = 19$)	All ($n = 42$)	P-Value
Sex	15 W / 8M	12 W / 7M	27 W / 15M	
Age, years	40.8 ± 12.8	38.1 ± 12.7	39.6 ± 12.6	
Height, cm	173.5 ± 10.6	175.7 ± 8.8	174.5 ± 9.8	
Weight, kg	87 ± 17.7	85.4 ± 15.1	86.3 ± 16.4	
Body mass index, kg/m^2	28.9 ± 5.3	27.7 ± 4.4	28.3 ± 4.9	
Central Sensitization Inventory (0–100)	31± 4.8	48.7 ± 8.7	39.0 ± 11.2	< 0.01
Patient-reported Pain Intensity (VAS, 0–10)	5.5 ± 2	5.2 ± 1.8	5.4 ± 1.9	
Disability (PDI, 0–70)	33.6 ± 11.2	26.8 ± 11.9	31.0 ± 11.7	
Physical Functioning (Rand36-PF, 0–100)	49.8 ± 22.3	63.3 ± 16.1	54.7 ± 21.1	
Catastrophizing (PCS, 0–52)	16.3 ± 8.9	20.3 ± 11.1	18.1 ± 10	
Injustice (IEQ, 0–48)	15.2 ± 8.9	18.5 ± 8.5	16.7 ± 8.8	
Psychological Traits Screening (BSI, t-score)	34.4 ± 4.9	41.5 ± 5.8	37.6 ± 6.4	= 0.01

Except sex, all results represent mean ± standard deviation. CLBP-, CLBP+: patients with chronic low back pain with low (-) and moderate-high (+) central sensitization levels. W: Women; M: men. VAS: visual analogue scale. PDI: pain disability index. Rand36-PF: Rand 36-Physical Functioning subscale. PCS: pain catastrophizing scale. IEQ: injustice experience questionnaire. BSI: brief symptom inventory.

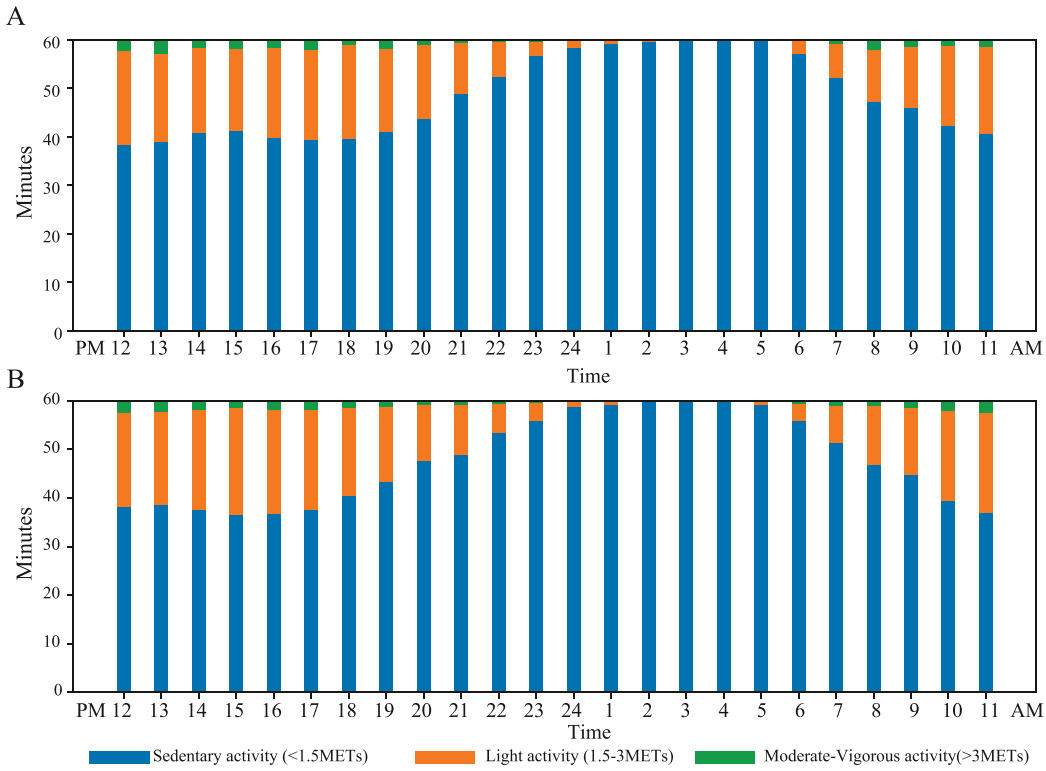

Fig. 2. Overall physical activity intensity levels of each hour during a day, based on the cut-points approach, of (a) CLBP- group and (b) CLBP+ group. CLBP-, CLBP+: Patients with chronic low back pain with low (-) and moderate-high (+) central sensitization levels.

poor work ability. Their PCS scores [39] and IEQ scores [40] were lower than the clinically relevant level.

Because 23 patients with CLBP- and 19 patients with CLBP+ were included and 4 segments of every patient were randomly selected, 92 (29 on weekend) and 76 (24 on weekend) acceleration segments were used for the cut-points approach and for training of HSMMs for CLBP- and CLBP+ respectively.

3.2. Results from cut-points approach

Based on the cut-points approach, no statistically significant differences were found in the averaged PA intensity levels calculated over every hour of the day or over the whole day ($p = 0.87$) (see Fig. 2).

3.3. Results from HSMM

The 4, 5, 6 hidden states HSMM were considered and BIC scores were computed. Taking the model fitting, model complexity, and model uncertainty into consideration, the number of hidden states was set to 5. More details are shown in Appendix E.

After the HSMMs training, the model parameters (emission probability, duration probability, and transition probability) were learned from the data.

3.3.1. Emission probabilities of hidden states

The emission probability distributions (modeled as Gaussian distributions) of hidden states 1 to 5 showed clear separation, with mean values dispersing approximately from 0 to 80 milligravity (mg). The differences of corresponding hidden states between CLBP- and CLBP+ were assessed by JSD values. All the JSD values are close to 0, suggesting similar emission probability distribution (see Table 2). Therefore, a direct comparison of hidden state sequences between the groups is allowed.

For both groups, the mean acceleration values of hidden state 1 were close to 0 mg which implied that patients were inactive, such as lying down (≈ 1.0 METs). The mean acceleration values of hidden state 2 were lower than 10 mg and may correspond to sedentary activities, such as desk work (≈ 1.3 METs). For hidden state 3, the mean values of acceleration were relatively low (smaller than 30 mg) and therefore, patients were assumed to do light PA during this state, for example, standing with manual applications (≈ 2.0 METs).

Based on the detection of walking events, it was shown that hidden states 4 and 5 contained 82.3% of the total walking events (35.9% and 46.4%, respectively), with walking speeds of 1.18 and 1.33 m/s, respectively. The speed of walking events in the hidden state 4 was lower than 1.25 m/s, so the hidden state 4 was interpreted as light locomotion state. The mean walking speed in hidden states 5 was within 1.25–1.43 m/s (1.33 m/s). It corresponded to 3.5 METs and was interpreted as moderate-vigorous PA state (> 3.0 METs).

Table 2
Emission probability distribution per hidden state and Jensen–Shannon divergence of hidden state distribution between CLBP- and CLBP+.

Group	CLBP-		CLBP+		
	Mean (mg)	SD	Mean (mg)	SD	JSD
State 1	0.19	0.76	0.8	4.85	0.31
State 2	6.37	4.91	8.46	6.69	0.04
State 3	20.84	7.31	25.96	12.95	0.08
State 4	40.17	12.57	44.88	9.21	0.05
State 5	63.47	55.38	83.01	52.89	0.02

CLBP-, CLBP+: patients with chronic low back pain with low (-) and moderate-high (+) central sensitization levels. SD: standard deviation. JSD: Jensen–Shannon divergence.

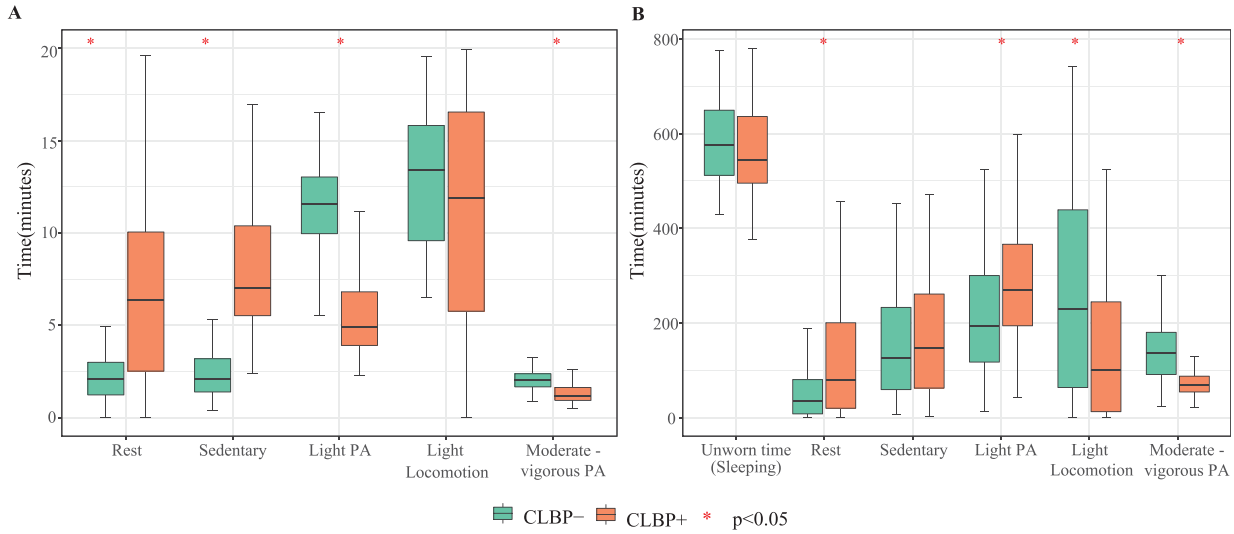

Fig. 3. Boxplots for (a) Bout duration of each hidden state, (b) Accumulated time of each hidden state and unworn time in a day. CLBP-, CLBP+: Patients with chronic low back pain with low (-) and moderate-high (+) central sensitization levels. P value obtained by T-test.

Therefore, the 5 hidden states were specified as rest state (≈ 1.0 METs), sedentary state (≈ 1.5 METs), light PA state (≈ 2.0 METs), light locomotion state (≈ 2.0–3.0 METs), and moderate-vigorous PA state (>3.0 METs).

3.3.2. Duration and accumulation time of hidden states

Comparing the bout duration time of hidden states between the two groups, CLBP- group exhibited a significantly shorter bout duration in the rest state ($P < 0.001$) and the sedentary state ($P < 0.001$). This group stayed for a longer bout duration in the light PA state ($P < 0.001$) and the moderate-vigorous PA state ($P < 0.001$) (see Fig. 3(a)).

In a day, the CLBP- group spent less accumulated time in the rest state ($P = 0.002$) and the light PA state ($P < 0.001$) and spent more time in the light locomotion state ($P = 0.002$) and the moderate-vigorous PA state ($P < 0.001$) (see Fig. 3(b)). Because CLBP- and CLBP+ groups spend a similar accumulated time in the sedentary activity state ($P = 0.4$) in a day, but CLBP- group had a shorter bout duration in the sedentary activity state, the CLBP- group had more frequent and shorter sedentary states. This was also shown in the transition probability matrixes.

3.3.3. Transition probabilities of hidden states

The statistical differences in transition probabilities between CLBP- and CLBP+ groups show that the CLBP- group had more frequent transitions from the rest, light PA, and moderate-vigorous PA states to the sedentary state (with $P < 0.001$). The CLBP+ group, on the other hand, had more frequent transitions from rest, sedentary, light PA, and moderate-vigorous PA states to the light PA state and or the moderate-vigorous PA state (with $P < 0.001$) (see Table 3, in red). Higher transitions from the light PA and moderate-vigorous PA states to the sedentary state may suggest that patients with CLBP- performed more frequent rest after being active. On the contrary, patients with CLBP+ had higher transitions from the active states (light PA and moderate-vigorous PA states) to other active states (moderate-vigorous PA states and light PA), which may suggest that they more often persist for a long period of activity.

To further investigate whether the patients in the CLBP+ group persisted a longer bout of activity than those in the CLBP- group, the light PA, light locomotion, and moderate-vigorous PA states were merged into a new state, named active state. The rest and sedentary states were merged as the inactive state. Fig. 4 shows that CLBP+ group persisted significantly longer in both the inactive ($P < 0.001$) and active states ($P = 0.037$) than CLBP- group.

3.3.4. Group and individual levels HSMM information

The group level accumulated time of each hidden state and transition probabilities between hidden states can be graphically organized as a HSMM graph, or signature of the group; as shown in Fig. 5. Every circle represents a hidden state, and the area of the circle represents the accumulated time in a day. The figure shows that in the CLBP- group, the sedentary state was the most frequent present state (with 5 red arrows) while in the CLBP+ group, there were more red arrows between active states.

Apart from visualizing the outcomes of HSMM at the group level, it can also provide details about individual level's hidden states organization information, the PA fingerprints (two examples are shown in Appendix F).

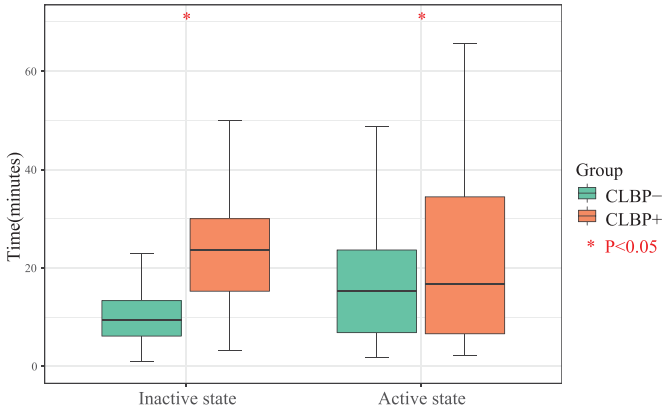

Fig. 4. Bout duration of inactive state and active sate of CLBP- and CLBP+ groups. CLBP-, CLBP+: Patients with chronic low back pain with low (-) and moderate-high (+) central sensitization levels. P value obtained by T-test.

Table 3
Transition probability matrix of CLBP- and CLBP+ groups.

From State	Group	To Hidden State				
		Rest	Sedentary	Light PA	Light locomotion	Moderate-vigorous PA
Rest	CLBP-	–	0.88	0.01	0.01	0.11
	CLBP+		0.40	0.21	0.00	0.38
Sedentary	CLBP-	0.39	–	0.10	0.03	0.47
	CLBP+	0.27		0.37	0.01	0.35
Light PA	CLBP-	0.01	0.42	–	0.14	0.42
	CLBP+	0.01	0.15		0.07	0.71
Light locomotion	CLBP-	0.01	0.14	0.17	–	0.67
	CLBP+	0.01	0.02	0.44		0.52
Moderate-vigorous PA	CLBP-	0.05	0.60	0.13	0.20	–
	CLBP+	0.10	0.13	0.68	0.09	

CLBP-, CLBP+: Patients with chronic low back pain with low (-) and moderate-high (+) central sensitization levels. Statistically significant differences are printed in red ($P < 0.05$).

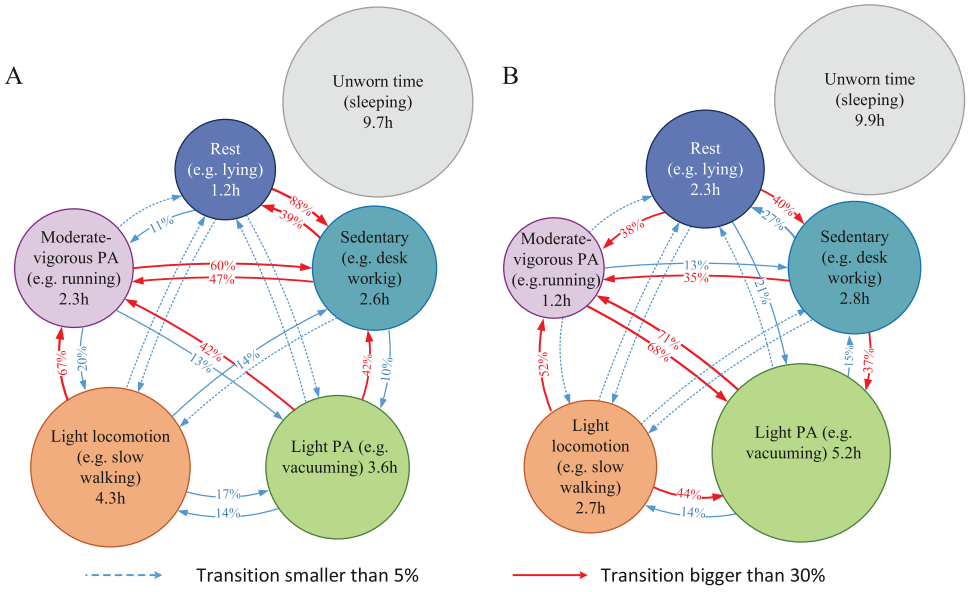

Fig. 5. Five states graphs (and unworn time) of (a) CLBP- and (b) CLBP+. CLBP-, CLBP+: Patients with chronic low back pain with low (-) and moderate-high (+) central sensitization levels. The arrows between 2 circles represent the transition probability (in percentage) between these 2 corresponding circles. When the transition probability is higher than 30%, the arrow is colored red. HSMM: Hidden semi-Markov models.

4. Discussion

The aim of this study was to explore in detail the relationship between PA, CS, and CLBP by analyzing the temporal organization of and transition between PA intensity levels (PA intensity patterns) using HSMM. While the conventional cut-points approach did not show significant differences in averaged or overall PA intensity levels between the CLBP- and CLBP+ groups in a day, the data-driven approach, HSMM, revealed different PA intensity patterns between the two groups. The CLBP- group had a significantly shorter bout duration of the sedentary state and higher transition probabilities from the rest, light PA, and moderate-vigorous PA states to the sedentary state. On the contrary, the CLBP+ group exhibited a longer bout duration of the active state and higher transition probabilities between active states (light PA state, light locomotion state, and moderate-vigorous PA state) and longer bout duration of inactive states (rest and sedentary states).

Significant differences in temporal organization of and transition between PA intensity levels may suggest that patients with CLBP- and CLBP+ had different PA intensity patterns. The CLBP- group exhibited higher transition probabilities from the light PA and moderate-vigorous PA states to the sedentary state, and had shorter bout durations of the sedentary state compared with CLBP+ group. These findings may imply that patients in the CLBP- group broke tasks into smaller bouts and took frequent and short rests. Alternatively, patients in the CLBP+ group exhibited higher transition probabilities between active states and had longer bout durations of the active and inactive states. This may imply that patients in the CLBP+ group exhibited a prolonged period of activity engagement and had a long period of rest. The PA intensity pattern of the CLBP+ group may be in line with the endurance [47] type from the Avoidance-endurance model (AEM) [15]. AEM postulated that a subgroup of patients shows a pattern of fear-avoidance responses caused by high catastrophizing, fear of pain, and avoidance behavior; another subgroup of patients shows a pattern of

endurance responses with overuse and overload of physical structures, despite having pain. The PA intensity pattern of patients in the CLBP- group may not be assigned to fear-avoidance responses because of the lower PCS score; although frequent short rests are regarded as an avoidance strategy [48] to some degree. The AEM distinguishes 2 types of endures responses, namely: distress-endure (DE), who tend to have more pessimistic thoughts and feel more negative, and eustress-endures, characterized by a positive mood. Endurance responses were assumed to exhibit a prolonged period of activity engagement which is in line with the results of the CLBP+ group. The higher BSI score may suggest that patients with CLBP+ adopted the DE pattern. However, because the data in this study were derived from a larger study which lacks the measurements of fear-avoidance beliefs and distress-endurance (e.g. avoidance-endurance questionnaire), the interpretation of the association between PA intensity patterns and the AEM model should be treated with caution. Consistent with others, the conventional cut-point approach with summary statistics analysis was not sufficiently sensitive to observe differences in objective PA levels [18]. The HSMM and analytic strategy used in this study show the potential to gain a better understanding of the relationship between daily PA intensity patterns, CS, and psychosocial factors, such as fear-avoidance or catastrophizing beliefs.

The findings of the current study do not support or refute the hypothesis that because of higher catastrophizing thought, fear of pain, or pain, patients with higher CS exhibit a fear-avoidance pattern. In the present study, catastrophizing thoughts and self-reported pain intensity between the CLBP+ and CLBP- groups were not significantly different. This finding is in line with the results of a previous study that observe that the majority of maladaptive responses in CLBP are characterized by endurance instead of fear-avoidance (i.e. 35.6% vs 9.6%) [49].

The current findings may imply the existence of the "bottom-up" type of CS in patients of the CLBP+ group [12]. Patients with the DE response pattern might expose the muscles to continuous stress and repetitive strain causing microdamage, laxity, and inflammation [50]. Ongoing nociceptive input may drive CS, which could explain why patients in the CLBP+ group with DE pattern exhibited a higher level of CS. The CLBP- group showed more resting in-between activity periods, which may contribute to partially remit features of CS because of the removement of ongoing nociceptive input [12], and consequently, CLBP- patients exhibited a lower level of CS. However, this study is cross-sectional, longitudinal studies are needed to gain insight in the causality or temporal relations between PA and CS in patients with CLBP.

No statistical differences were found in the accumulated time of the sedentary state between the CLBP- and CLBP+ groups. This finding supports evidence from previous observations that sitting time did not correlate with CS [51]. The overall intensity levels of PA over a day between the CLBP- and CLBP+ groups were not significantly different. Patients in the CLBP- group spent more time on the light-locomotion and moderate-vigorous PA states while patients in the CLBP+ group spent more time on the light PA state. These findings support the suggestion that the quality and intensity of activities instead of the overall amount of PA is associated with levels of CS in patients with CLBP [51].

The population with CLBP is heterogeneous. For effective clinical interventions, it is important to gain more knowledge about subgroups of patients in this group. HSMM is applied to identify subgroups based on their PA intensity patterns and these subgroups may be linked to pain-related features, such as CS. This will contribute to a better understanding of underlying functional mechanisms of the development and maintenance of chronic pain and pain-related disability. In the present study, HSMM can not only provide information at the group level about PA temporal association, but also generate PA fingerprints for individual patients. These fingerprints may help patients and clinicians visualize the patients' everyday PA organization. Based on the specific PA intensity patterns from the subject's fingerprint, clinicians may adjust therapy accordingly and personalization of interventions may increase the effectiveness of treatment.

5. Limitations

Although accelerometer devices can nowadays be commercially purchased at a low cost, algorithms and source code are available via open-source platforms, the data processing still requires advanced level of knowledge and skills that are typically not held by clinicians. Further developments should be geared toward making these analyses more user-friendly to enable routine clinical use. The present study derived hidden states from one accelerometer sensor for feasibility reasons. Using multiple sensors would provide more information, but may cause more effort on data collection (e.g. subjects may be reluctant to wear for an extended period of time because of uncomfortable). It should also be noted that a gold standard measure to diagnose CS is unavailable [52]. The CSI is a broad assessment tool to indirectly measure CS, because higher scores are associated with the presence of CS syndromes [37]. Fifty-three acceleration segments were collected during weekends and PA may vary across workdays and weekends. However, both groups had almost the same proportion of weekend data (30%). The weekend data may not affect the comparison. Lifestyle factors (e.g. type of physical activity, sleep quality, and work load) and psychosocial (e.g. stress; anxiety, depression, and pain catastrophizing) factors are contributing factors that exacerbate CS [51]. Identifying the relationship between these factors with CS and CLBP may help to identify the most important modifiable factors that influence CS. This remains an important topic for future studies.

6. Conclusion

In this study, the results showed that the CLBP- and CLBP+ groups had different PA intensity transition patterns. Patients in the CLBP- group had a higher transition probability from the rest, light PA, and moderate-vigorous PA states to the sedentary state and had a significantly shorter bout duration of the sedentary state. Conversely, Patients in the CLBP+ group exhibited longer duration of active and inactive states, and had higher transition probabilities between active states, which may support the suggestion that patients in the CLBP+ group adopted a DE pattern. The results of this study may contribute to a better understanding of the relationship between PA, CS, and CLBP and will contribute to improve personalized rehabilitation prevention and interventions, and the development of CLBP-specific physical activity guidelines.

HSMM is able to automatically cluster the PA intensity levels from accelerometer data and provide detailed information about temporal organization and transitions of PA intensity levels. Hence, it can recognize the differences between CLBP- and CLBP+ groups while the conventional cut-points approach is not sufficiently sensitive. This study highlights the potential use of HSMM in future research to explore the relationship between PA, CS, and CLBP, shedding a new light on the dynamics of PA intensity and transition patterns.

Declaration of Competing Interest

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personal relationships that could have appeared to influence the work reported in this paper.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.cmpb.2023.107432.

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