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Unraveling dynamics of human physical activity patterns in chronic pain conditions

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Chronic pain is a complex disabling experience that negatively affects the cognitive, affective and physical functions as well as behavior. Although the interaction between chronic pain and physical functioning is a well-accepted paradigm in clinical research, the understanding of how pain affects individuals' daily life behavior remains a challenging task. Here we develop a methodological framework allowing to objectively document disruptive pain related interferences on real-life physical activity. The results reveal that meaningful information is contained in the temporal dynamics of activity patterns and an analytical model based on the theory of bivariate point processes can be used to describe physical activity behavior. The model parameters capture the dynamic interdependence between periods and events and determine a 'signature' of activity pattern. The study is likely to contribute to the clinical understanding of complex pain/disease-related behaviors and establish a unified mathematical framework to quantify the complex dynamics of various human activities.

Pain is conceptualized as a subjective and multidimensional experience that both influences and is influenced by a wide range of biological, psychological and social factors[1]. When pain becomes chronic, it often has a detrimental effect on a person quality of life. The effective pain management begins with a comprehensive understanding of its causes and mechanisms. Over the last decades the medical and research communities have been struggling with the assessment of chronic pain conditions and have agreed that the main outcome domains are *pain intensity*, *physical functioning*, *emotional functioning*, and patient ratings of overall improvement[2]. *Physical functioning*, defined as observable physical limitations experienced by patient over a defined period of time, can be inferred from the monitoring of the daily *physical activity* (PA), i.e. all movements that an individual performs to achieve the activities of daily living. Compared to all other pain-related dimensions, which are based on self-reporting and are therefore inherently subjective, physical functioning/activity has the advantage of being quantifiable objectively.

Although the interaction between chronic pain and PA is a well-accepted paradigm in clinical practice, there is still the need for a methodological framework allowing a comprehensive assessment of daily functioning. The studies conducted during the last decade with the aim to quantify the relationship between pain and daily PA provided variable results depending on how and how precisely PA was assessed. A review of the results and limitations of these studies indicates that in addition to issues related to the measurement protocol (e.g. necessity for ambulatory long-term monitoring) an important aspect is the methodological analysis of raw data usually recorded with body-worn accelerometer devices[3,4]. The information provided by changes of specific activity parameters, for instance duration and type of body postures/activities or gait parameters (speed, cadence) has obvious clinical relevance[3,5,6] however it ignores important features of *dynamics* of human PA behavior[7,4]. The PA in real life is made of a large number of actions that are repeated in various and complex *patterns*, for which there is currently no quantitative definition of normality. In addition, a large number of factors including age, disease, the confinement due to work or otherwise, the response to unexpected events, and the deliberate decisions to perform specific tasks may significantly modify the PA pattern by changing the duration, frequency and timing of various body postures and activities. The methodological analysis must therefore focus on both, the quantitative aspects and the dynamical properties of activity patterns[4,7,8].

Recent research on the dynamics of human activity has suggested that long-term monitoring may allow for new insights into the temporal organization of PA patterns in health and disease. The suggestion is that normal

behavior is governed by scale invariance (statistical properties of fluctuations of PA patterns remain the same at different time-scales) and universal distribution laws[7,9–13]. Scale-invariant dynamic patterns have been found in fluctuations of the forearm motor activity[10], the posture allocation[7] and the gait[14] with long-range correlations on time scales of seconds to hours that are insensitive to either changes in mean activity level or to fluctuations caused by random and scheduled extrinsic factors[15]. This time-invariant dynamic patterns was associated with the healthy function (i.e., flexible behavior, capability of altering motor behavior to adapt to different task demands, and a possible regulation by central control mechanisms[9,14,16,17]), and it was shown to be affected by aging and by disorders such as Alzheimer's disease[10], chronic pain[7] and chronic fatigue syndrome[13]. Studies that have focused on the statistical distribution of forearm motor activity have found that the durations of activity periods (i.e., wrist acceleration counts above predefined thresholds) follow a universal stretched exponential cumulative distribution with characteristic time, which is not different in healthy subjects and patients with major depressive disorders. On the other hand, the durations of night resting periods follow a scale-free cumulative distribution with significantly lower scaling exponents in patients than in healthy subjects[12]. A few hypothesis were proposed to explain the intrinsic origin of universality and scale invariance in human behavior[9,10,12] however the complexity resulting from the interplay of specific behavioral tasks, different environments, and various social contexts makes it difficult to provide a comprehensive understanding.

Generally, the acquisition of scientific knowledge about a phenomenon/process necessitates the (1) measurement and data collection, (2) information extraction from data, and (3) interpretation of the information according to a theory/hypothesis. The current knowledge about how complex interactions between various factors may reflect a PA pattern that is specific to a condition/individual can be improved only with a research effort at each level, from data collection and information extraction to validation of theoretical frameworks able to explain the patterns in the data. Even though in chronic pain research significant progress was made with the conceptualization of different behaviors related to coping strategies (i.e. activity avoidance, persistence and pacing)[18–20], less is known about how specific strategies relate to actual PA patterns in daily life[20–23]. Given the above context, the aim of the present study is to contribute to the understanding of human PA patterns in chronic diseases/pain conditions by describing methodological analysis to extract relevant information from data collected under long-term real-life conditions. We hypothesize that appropriate tools, which are able to quantify the various parameters of PA and their interdependence, may objectively document if and how pain interfere and disrupt normal daily activity. Such tools may be useful in future prospective studies designed to validate the theoretical models of activity-related behavioral styles[18–23].

Detailed body movements recorded in patients suffering from intractable chronic pain and healthy subjects are used to accurately quantify PA in terms of posture allocation (i.e. sitting, standing, lying) and walking[24] (compared to the traditional wrist actimetry this assessment is more adequate to characterize the functional limitations due to chronic pain of different etiologies). With this information, the PA pattern is modeled as a *two-state process* by defining the successive, aggregated periods of standing and/or walking as *activity*, and sitting and/or lying as *diurnal rest* (the definition of sitting/lying as *rest* relates to the fact that all patients reported pain-related limitations of their walking perimeter; an alternative, more generic definition could be 'sedentary'[25]). The methodological approach used to analyze this pattern aims to reveal and quantify various embedded behavioral features: the total amount of time spent in *activity*/*rest,* the statistical distribution laws characterizing the periods of *activity* and *rest*, the relationship between the duration of successive *activity* and *rest* periods, and the dynamics of transitions between *activity* and *rest*. Finally, an analytical model able to incorporate the relevant observed features is formulated. The analysis is conducted on a large database in order to: *(i)* identify the features of PA patterns that better differentiate clinically significant chronic pain intensities; *(ii)* get a better understanding on the factors influencing the temporal organization of human PA patterns in health and disease; *(iii)* verify the capability of the analytical model to reliably capture the relevant PA features; *(iv)* discuss the results in the context of contemporary studies on statistical modeling of human dynamics[10–12,26–28].

Results

Collected data. The study includes 72 subjects (58 chronic pain patients and 14 healthy pain free individuals) who were monitored in real-life conditions during 5 consecutive days, eight hours per day. The patients estimated the intensity of their usual pain on a visual analogue scale (VAS) from 0 to 10. To quantify the impact of clinically different pain intensities (min 30% difference on VAS) on PA, independently of demographic covariates such as age and employment status, the subgroups are matched in two pairs and the comparison is performed as follows: *no pain* (VAS = 0, $n = 14$ subjects) vs. *severe pain* (VAS = 7 to 10, $n = 25$) in *middle age* groups and *moderate pain* (VAS = 4 to 6, $n = 14$) vs. *severe pain* in *old age* ($n = 19$) groups (Table S1).

Total time spent in *activity* and *rest*. Figure 1a shows an illustrative PA pattern as it unfolds over a period of monitoring time. Because chronic pain may interfere with physically demanding tasks, the usual assessment procedure is to quantify the amount/percentage of time spent in either PA states. The group-averaged results shown in Fig. 2a indicate that with higher pain intensities the amount of time spent in *activity* decreases significantly. Although this parameter indicates that pain intensity may have an impact on the amount of physically demanding activities it does not contain information about the dynamics of PA behavior, i.e. how the total amount of *activity* is distributed in periods over the time. Therefore, the next step is to search for a distribution model that characterizes the periods of *activity* (a) and *rest* (r) of individual subjects.

Distribution laws of *activity* and *rest* periods. The shape of empirically complementary cumulative distribution of diurnal *activity* and *rest* periods illustrated in Fig. 3 (mixture of a straight line and a slightly curved line as a parabola) suggests the *lognormal distribution* to be a suitable analytical model to fit the observed data[29]. Goodness of fit analysis conducted with other candidates indicates the lognormal distribution to be the best fitting model for more than 60% of data. For 30% of data the best fitting model is the double Pareto distribution (Pareto2) which falls between the lognormal and Pareto (see Supplementary Method S1, Table S1). The estimated scale (μ_x) and shape (σ_x) parameters of the lognormal cumulative distribution function (CDF), $F_x(x) = 1/2 erfc(-\ln x - \mu_x)/\sigma_x)$, indicate that there is a trend (statistically non-significant) towards increased variability in periods of rest and decreased variability in periods of activity when pain increases (i.e., high pain intensity increases the likelihood of longer rest periods and shorter activity periods) (see Supplementary Tables S2, S3). A possible explanation for this observation is that all included patients reported limitation for long continuous walking (see Methods, Study design and data collection).

Statistical distance between distributions of *activity* and *rest* periods. In the quest of unraveling clear differences in PA patterns, we consider the subject's dichotomous *activity-rest* allocation over the monitoring time (Fig. 1a) and quantify the statistical distances/differences between CDF of *activity* and *rest* periods, $F_a(x)$ and $F_r(x)$, respectively. Figures 4a,b show illustrative examples of estimated CDFs for a patient with a high pain score and a pain free healthy subject. To quantify the entire difference

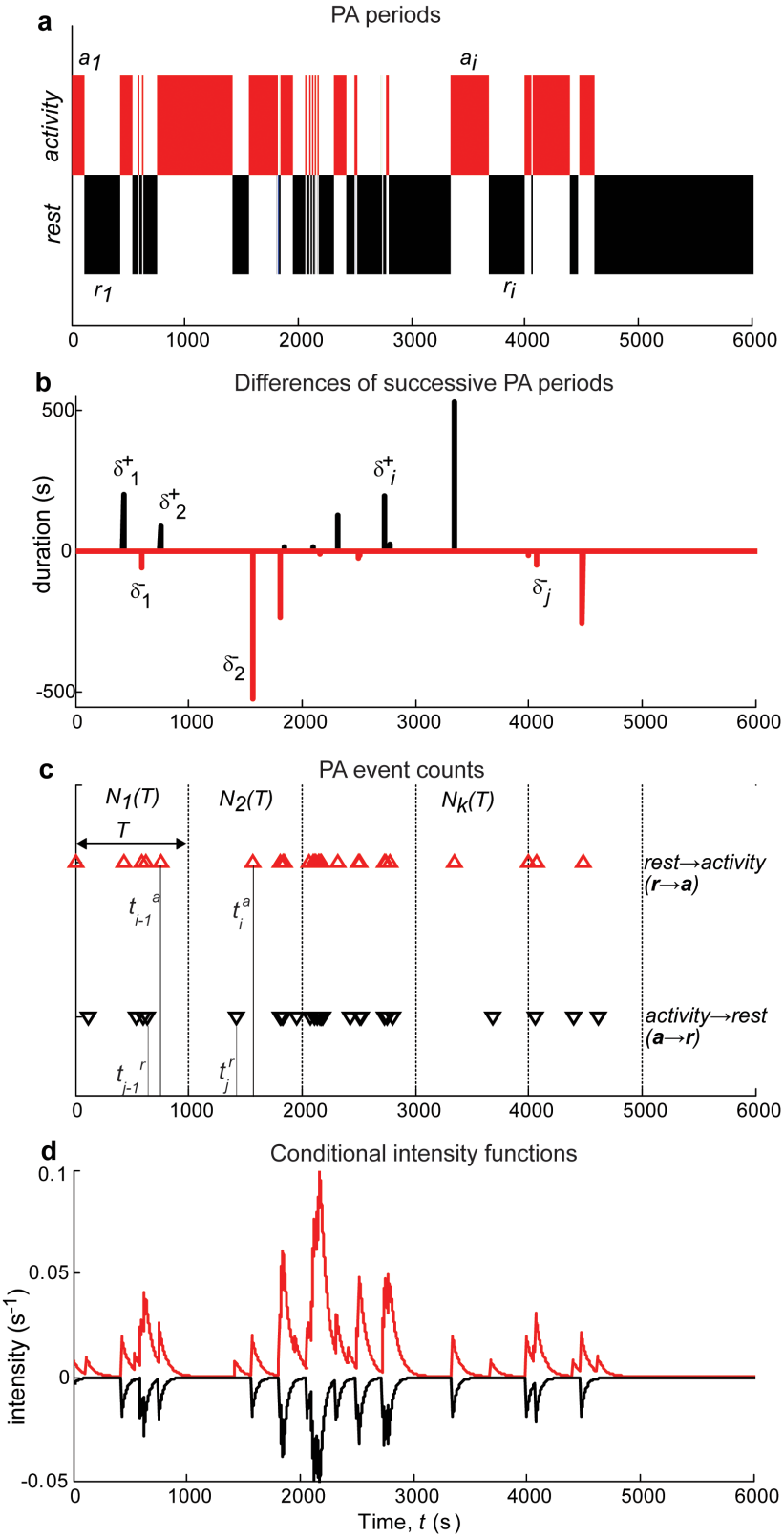

Figure 1 | Representation of information embedded in *PA* pattern as *periods* and *events*. (a) pattern of dichotomous PA states from which *PA periods* are defined as: *activity*, $\mathbf{a}=\{a_i\}$, $i=1,n$, *rest*, $\mathbf{r}=\{r_i\}$, $i=1,n$, and *activity-rest succession (pattern 'ar')*, $\mathbf{ar}=\{a_1r_1a_2r_2,\ldots,a_ir_i\}$, $i=1,n$; (b) pattern of differences between successive periods of *activity* and *rest* from which PA periods are defined as: *amount of excess rest following the previous activity*, $\boldsymbol{\delta}^+=\{r_i-a_i\}$, $r_i\geq a_i, i=1,n$, and *amount of deficit in rest following the previous activity*, $\boldsymbol{\delta}^-=\{r_i-a_i\}$, $r_i<a_i, i=1,n$; (c) pattern of $a\rightarrow r$ and $r\rightarrow a$ *transitions represented as event series and event counts*, $N(T)=\{N_k(T)\}$, $k=1,M$, where $N(T)$ denotes the counting function of the pooled process which assembles and orders the occurrence time of $a\rightarrow r$ and $r\rightarrow a$ transitions; (d) conditional intensity functions $\lambda_a(t|H_t|)$ and $\lambda_r(t|H_t|)$ (inverted to aid visualization), who model the dependencies between the timings of $a\rightarrow r$ and $r\rightarrow a$ transitions. Note that this illustrative example is extracted from the PA pattern of one subject.

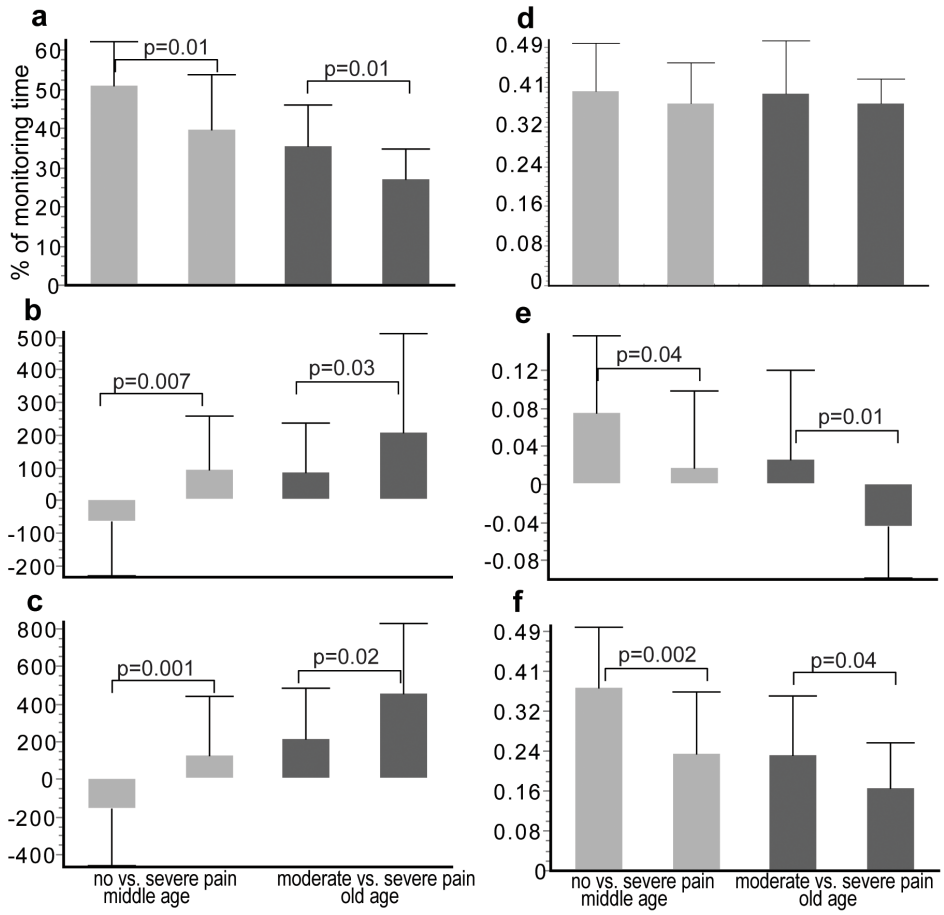

Figure 2 | Parameters quantifying the PA pattern. (a) the cumulated activity level (overall time spent in activity), *activity(%);* (b) the area between CDF of *activity* and *rest* periods, A_{ar}; (c) the area between CDF of differences δ^- and δ^+, A_δ; (d) the burstiness parameter B; (e) the 1st order serial correlation coefficient between successive *activity* and *rest* periods (memory coefficient) M; (f) the Fano factor scaling exponent ω_F, quantifying multi-scale burstiness of PA events/transitions.

between the CDFs we use the area test statistic defined as $A_{ar} = A_{Fa}^{over} - A_{Fr}^{over}$ where A_{Fa}^{over} and A_{Fr}^{over} represent area over $F_a(x)$ and $F_r(x)$ respectively, calculated by trapezoidal numerical integration. A positive value for A_{ar} indicates that $F_a(x)$ is above $F_r(x)$, i.e., over ensemble the *activity* periods are shorter compared to the *rest* periods while a negative value indicates $F_r(x)$ above $F_a(x)$, i.e., the *rest* periods are shorter than *activity* periods.

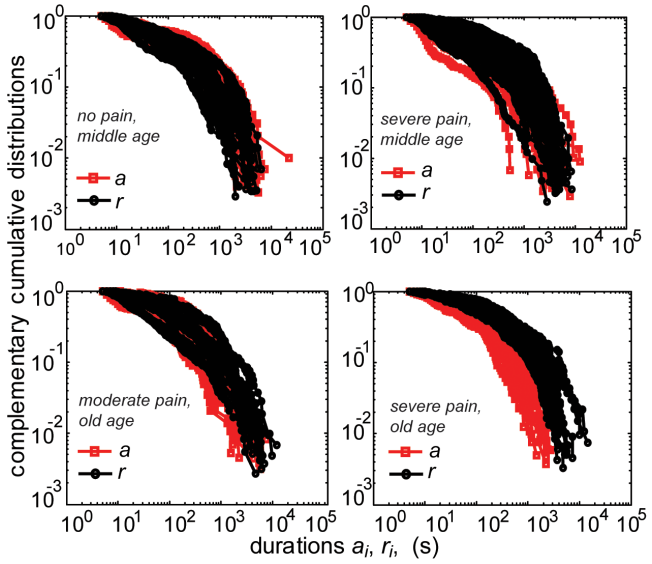

Figure 3 | Complementary cumulative distribution (log-log plot) of *activity* and *rest* periods, estimated for each subject in the four groups.

The computations show that area A_{ar} increases with pain intensity and discriminates significantly between the compared groups (Fig. 2b). It should be pointed out that A_{ar} provides a better discrimination between patients with and without pain than the total amount of *activity*, especially in middle age subjects. This suggests that individuals with different pain intensities have different allocation pattern of the *activity* and *rest* periods (Fig. 1a), despite similar cumulated time. For instance, the same amount of *activity* can be cumulated in different ways - from a few longer periods or from many shorter periods or from a combination of both. Multiple regression analysis (all subjects, $n = 72$) indicates that a significant amount of the variance in *activity*(%) parameter ($R^2 = 60\%$, $p < 0.0001$) is associated with the total number of *activity* to *rest* and *rest* to *activity* transitions, *NT*, ($\beta = 0.06$, *t-ratio* $= 4.7$, $p < 0.0001$) and the area A_{ar} ($\beta = -0.03$, *t-ratio* $= 6.3$, $p < 0.0001$). Relevant pain-related behavioral features are therefore likely to reside in the *temporal dynamics* of PA patterns i.e. in the manner in which *activity* and *rest* periods are interwoven throughout daily-life.

Relationship between successive *activity* and *rest* periods. It makes intuitive sense to assume that the duration of resting time after a physically demanding activity increases in conditions such as chronic pain (and/or fatigue, old age), and consequently, it is relevant to study the differences between the duration of successive *activity* and *rest* periods.

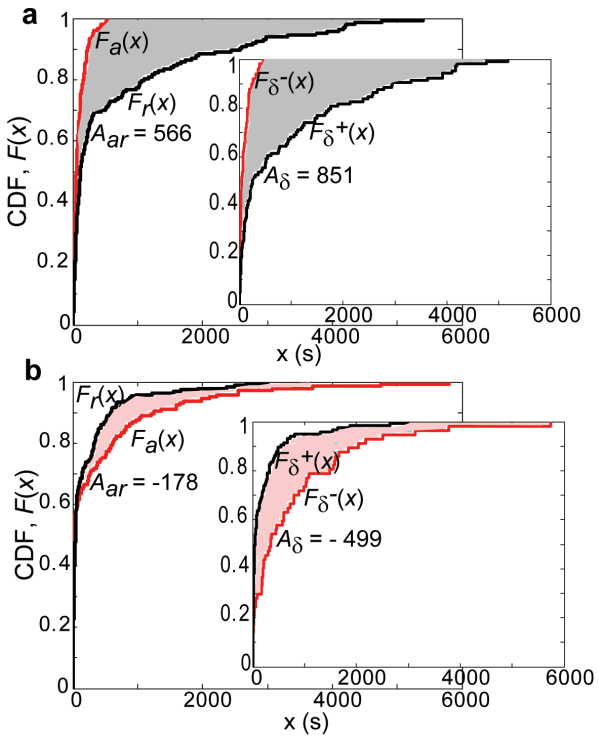

Figure 4 | Illustrative example of statistical distances between distributions of *activity* and *rest* periods (δ^+ and δ^- in the inset), quantified with the area test statistics (color-area) for: (a) a patient with high pain level (VAS = 7.4) and (b) a healthy pain free subject (VAS = 0). The higher positive value of A_{ar} (A_δ) for the chronic pain patient indicates that in ensemble, activity periods are shorter than resting periods while the negative A_{ar} for the healthy pain free subject indicates that activity periods are longer than resting periods.

The sequence of differences $\delta_i = r_i - a_i$, $i = 1,\ldots,n$ (Fig. 1a, b) is divided into subsequences δ^+ and δ^- depending on whether the *rest* period is longer or shorter than the preceding *activity* period, that is: $\delta_i \in \{\delta_k^+\} \Leftrightarrow r_i \geq a_i$ and $\delta_i \in \{\delta_l^-\} \Leftrightarrow r_i < a_i$ (r_i following a_i). As with the periods of *activity* and *rest*, the best fit for CDF of δ^+ and δ^- is obtained with the lognormal distribution (see Supplementary Table S1). The analysis shows that the area between CDF of δ^+ and δ^-, denoted by A_δ, increases (i.e., *rest* periods following *activity* periods are longer) when the intensity of pain increases, indicating slightly better differentiating properties than A_{ar}, as illustrated in Fig. 2c and Fig. 4a, b (inset).

The main observation from these results is that *activity* and *rest* periods, and their successive differences follow long-tailed distribution suggesting inhomogeneous/bursty dynamics of PA pattern. This point out to three fundamental questions addressed in the following: *(i) how can be such inhomogeneous temporal dynamics of PA behavior quantifie*d, *(ii) why does it occur and (iii) how to specify it into a mathematical analytical model.*

Temporal dynamics of PA pattern: correlations and burstiness. Theoretically, two different mechanisms may be at the origin of inhomogeneous/bursty dynamics of PA pattern (Fig. 1a): *(1)* the correlations between successive *activity* and *rest* periods, and *(2)* the high variability of their duration indicated by the long-tail of fitted distribution[30]. Correlations between successive periods are estimated with the 1st order serial correlation/memory coefficient, M (Methods). The modest positive values of M indicate a tendency for long (short) *activity/rest* periods to be followed by long (short) *rest/activity* periods and this trend is accentuated in patients with low pain scores (Fig. 2d). The negative mean value in the *severe pain*, *old age* group suggests that in elderly patients with high pain scores there is a tendency for short *activity* periods to be followed by long *rest* periods (the vice-versa, i.e., long *activity* followed by short *rest* is not supported by the values of A_δ).

The variability of PA pattern is quantified with the normalized coefficient of variation defined as the burstiness coefficient, B (Methods). The observed trend is toward a reduced but not statistically significant variability of *activity-rest* sequence when pain increases (Fig. 2e). This can be explained by the fact that the value of B increases because of two opposite factors: the large tail of the distribution of *activity* periods (more common with low pain intensity) and/or the large tail of the distribution of *rest* periods (more common with severe pain conditions).

It is worth mentioning that when B and M parameters characterizing PA patterns are represented in the (M, B) space, the dynamics of these patterns is consistent with those of other human activities[30], as illustrated in Fig. 5.

Temporal dynamics of PA pattern: multi-scale correlations and burstiness. Further insight into the dynamics of PA pattern can be obtained from the quantification of long-term multi-scale correlations of *activity to rest* ($a \rightarrow r$) and *rest to activity* ($r \rightarrow a$) transitions defined as point-processes, i.e. the timing of transitions (t_i^a, t_j^r, $i = 1,..,n, j = 1,...,m$) are modeled as *events* on the monitoring time-axis (Fig. 1c). The interesting question with this representation is whether the events of the pooled process ($t_i^a \bigcup t_j^r$) occur randomly, i.e. uncorrelated, or in bursts (and burst-within-bursts), i.e. correlated over many time-scales. The statistical measure used to distinguish multi-scale burstiness from random behavior is the Fano factor[31], defined as the variance to mean ratio of the number of events in time windows of specified length T (Methods). The analysis indicates that the Fano factor scaling exponent, denoted by ω_F, decreases significantly with increased pain severity (Fig. 2f). Higher values of ω_F suggest that the PA events occur in bursts and this pattern holds over several time scales. Conversely, lower values of ω_F indicate that transitions appear more randomly distributed over the monitoring time.

To understand the possible origin of the multi-scale burstiness and its behavioral consequences we investigate the relationship between the metrics that quantify the dynamics of PA pattern. For any given point process, the inter-event periods and the event counts statistics are closely related, as indicated by the analytic equation of Cox & Lewis[32] expressed as: $\lim_{T\to\infty} F(T) = CV^2(1 + 2\sum_{i=1}^{\infty} SC_i)$. In our case, CV is the ratio of the standard deviation to the mean of *activity-rest (**ar**)* sequence illustrated in Fig. 1a, and SC_i denotes the i^{th} serial correlation coefficients of ***ar*** sequence. According to this equation we explore the Fano factor scaling exponent ω_F as a function of the burstiness parameter B (normalized CV), and the memory coefficient M (1st order SC): multiple regression analysis ($n = 72$) indicates that a significant amount of the variance in ω_F ($R^2 = 40\%$, $p < 0.0001$) is associated with B ($\beta = 0.64$, *t-ratio* $= 4.1$, $p = 0.0001$) and M ($\beta = 0.54$, *t-ratio* $= 3.3$, $p = 0.001$). The memory coefficient M (and implicitly ω_F) decreases when area A_δ increases ($r = -0.67$, $p = 10^{-10}$), i.e. when longer *rest* periods succeed to *activity* periods. The suggestion is that the multi-scale burstiness features may reflect the capacity of a subject to balance the duration of successive *activity* and *rest* periods (positive M) including the ability to perform long periods of activity followed by short rest (smaller/negative A_δ). In the elderly and in chronic pain patients the bursty PA pattern breaks down, presumably because systematically longer rest periods are needed to recuperate after an episode of demanding activity (negative/zero M). It should be pointed out that the bursty PA pattern can also be broken by increased yet abnormal PA qualified as 'overactive/endurance' behaviors[19,20]. In this case, a decreased/negative value of M describes *rest* periods that are consistently shorter than their preceding *activity* periods.

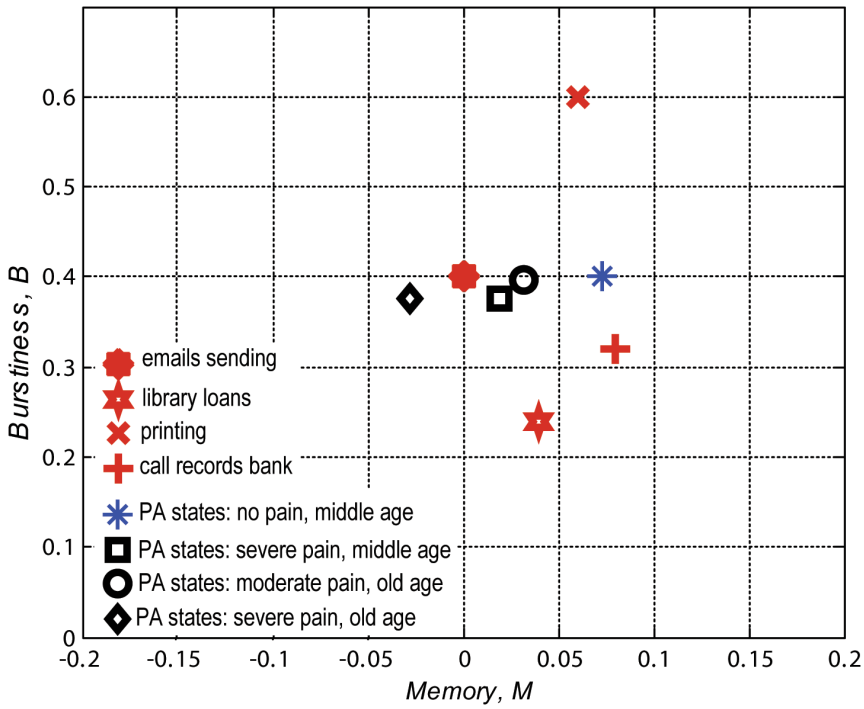

Figure 5 | Human PA pattern in the Memory-Burstiness (*M, B*) phase diagram. Recent studies in statistical physics community showed that the pattern of various human activities such as email and phone communications, web browsing, library visitation, etc., is characterized by long-tailed distributions of inter-event intervals and burstiness, for which various generating mechanisms were proposed. Our analysis reveals that human daily-life PA patterns locate in the same area in the *(M, B)* space however, with advanced aging and disease (severe pain), the PA patterns shift from the common area.

An additional insightful view on the possible origin of the multi-scale burstiness can be obtained by exploring the relation between the timing of PA events using surrogate data analysis (see Supplementary Method S2, Table S4). This analysis demonstrate that for the pain-free group the multi-scale burstiness properties are essentially due to positive correlations among events, associated with the specific ordering of *activity* and *rest* periods and, to a lesser extend to the distribution of *activity* and *rest* periods themselves. Conversely, for the chronic pain groups the surrogate data analysis indicates no correlation among events in the original data therefore the values of ω_F are mainly related to the long-tailed distribution of *activity* and *rest* periods.

Statistical modeling of PA pattern: bivariate point process model. In order to formulate a mathematical model capable to capture the dynamics of PA patterns we consider the sequences generated by the timing of transitions $r \rightarrow a$, $\{t_i^a\}, i=1,\ldots,n$ and $a \rightarrow r$, $\{t_j^r\}, j=1,\ldots,m$ as a *bivariate stochastic point process* (Fig. 1c). A point process able to model burstiness/clustering and correlations in a parsimonious way is the Hawkes bivariate (mutually exciting) point process (HBPP) with exponential decay[33,34]. The HBPP is described by the conditional intensity functions $\lambda_a(t|H_t)$ and $\lambda_r(t|H_t)$ (equation 1, Method) which represent the instant probabilities of $r \rightarrow a$ and $a \rightarrow r$ transition occurrences given the previous realizations (history H_t). The most important quantities of HBPP in the context of our modeling are the averaged conditional rates $\hat{\lambda}_a$ and $\hat{\lambda}_r$, and the cluster sizes c_a and c_r (equation 2, Method).

Goodness of fit analysis demonstrates that the model fits accurately (95% CI) for all subjects (see Supplementary Method S3, Table S5, and Figures S1-S72). The descriptive properties of the model are evaluated using the multiple/bivariate regressions between the empirical parameters describing the PA pattern and the estimated HBPP model parameters. The variance in the empirical number of transitions *NT* is significantly explained ($R^2 = 82\%$, $p < 0.0001$) by the model averaged conditional rates $\hat{\lambda}_a$ ($\beta = 74981$, *t-ratio* $= 12.7$, $p < 0.0001$) and $\hat{\lambda}_r$ ($\beta = 29804$, *t-ratio* $= 3.7$, $p = 0.0004$). The variance in the burstiness parameter *B* is significantly associated ($R^2 = 63\%$, $p < 0.0001$) with the cluster size c_a ($\beta = 0.052$, *t-ratio* $= 9$, $p < 0.0001$) and c_r ($\beta = 0.007$, *t-ratio* $= 2.1$, $p = 0.03$), while the variance in the memory parameter *M* is moderately but significantly explained ($R^2 = 42\%$, $p < 0.0001$) by the cluster size c_a ($\beta = 0.04$, *t-ratio* $= 6.5$, $p < 0.0001$) and c_r ($\beta = -0.02$, *t-ratio* $= 4.7$, $p < 0.0001$). The amount of *activity* (%) and the area A_δ are significantly associated with $\hat{\lambda}_a$ ($r = 0.7$, $p < 0.0001$ and $r = -0.6$, $p < 0.0001$, respectively). These values indicate that the HBPP can be used as a unified stochastic model of the various dynamical features of PA pattern.

Discussion

Quantitative parameters such as the time spent walking or standing (*activity*) can be useful metrics - and make intuitive sense - when assessing PA. However, measuring *activity* (or *rest)* as percentages of the monitoring time does not capture information regarding the *activity-rest* temporal pattern, for example, does not distinguish between a large number of short periods and a small number of long periods – two situations with different underlying dynamics. The results of this study provide empirical evidence that clinically relevant information may be contained in the way the durations of *activity* and *rest* (sedentary) periods are distributed in everyday life. This is illustrated by the fact that the parameters quantifying the dynamics of PA pattern (i.e., A_{ar}, A_δ, *M*, ω_F) are more discriminative than *activity(%)* (Fig. 2). However, none of these parameters shows a complete non-overlap between the compared groups which signifies that some individuals with high pain intensity may display a PA behavior similar with free/low pain subjects (either in terms of total cumulated *activity(%)*, dynamics of pattern, or both). These findings seem to support the conceptualization of chronic pain as an intricate relationship between physiological and psychological factors with

impact on the triad physical, emotional, and social functioning. The suggestion is that the patterns of daily life activity may be modulated not only by pain intensity but also by emotional/psychological factors such as the ability to develop behavioral coping strategies[18]. The 'fear-avoidance' of activity is the most popular pain-behavioral model however recent data suggest that more complex behaviors are equally appropriate: the 'pacing' which consists of repeated rest breaks that presumably help to complete activities, and 'endurance/over-activity' where high rate activity patters are supposed to help to get things done despite pain[20]. Although these assumptions need to be validated in larger future prospective studies, designed to include in addition to PA monitoring adequate avoidance-endurance questionnaires[19], the presented methodological framework (which quantify both the quantity of *activity* as well as the dynamics of PA pattern) has the potential to objectively reveals such complex behaviors (see Fig. 6). The approach could be useful in the context of the studies initiated in psychobiological pain research[19,20] as well as for diagnostic and personalized therapy since circumstantial evidence suggest that excessive avoidance behavior and excessive endurance behavior may lead to increased disability levels through different mechanisms[18,20].

The results of our study may also contribute to the understanding of PA behavior in the context of the current research on human dynamics. The analysis shows that the timing of $a \rightarrow r/r \rightarrow a$ transitions follows non-Poissonian statistics characterized by a bursty pattern, and the durations of *activity* and *rest* periods display long-tailed distributions. Recent studies indicated that the bursty patterns arising from long-tailed distributions (i.e. power-law, lognormal, stretched exponential) and/or the temporal correlations between inter-event periods are common in many human activities such as sending e-mails[26,27,35], visiting libraries, web-browsing[28], trading in a stock market[36] or initiating arm-movements[12]. Our results reveal that durations of *activity* and *rest* periods are characterized by similar long-tailed distributions, and the parameters of lognormal fitted model vary with pain intensity (and aging). Long-tailed distributions were frequently used to describe statistics of complex systems, i.e., systems with multiple interaction units[30,37]. In the context of the present study we can postulate that the overall dynamics of human PA patterns is determined by aggregated effects of competing factors related to the patient (e.g. pain intensity, fear of movement, fatigue, coping strategies) as well as to the environment (e.g. work, reaction to unforeseen events, daily tasks). When pain increases over a certain threshold, the patient-related factors (i.e., pain) may prevail over physically demanding task resulting in interruption of activity or the need for longer recuperation periods or both. The statistical distance between the distributions of the periods quantifying the excess of or deficit in rest after an activity period (A_δ) is one of the parameters that provide the best distinction among patients with different pain intensities.

The temporal dynamics observed for PA patterns appears also to be consistent with dynamics of other human initiated actions[30]. Several mechanisms have been proposed to explain the temporal bursts of the various actions including rational decision making processes that result in prioritizing the tasks[26], the memory effects[28], and the varying/adaptive interest[38] whereby human behavior is influenced by prior experience. There is however, no evidence suggesting that such mechanisms could explain the bursty pattern of PA (initiation of $a \rightarrow r/r \rightarrow a$ *transitions)*. Instead the results may contribute to understand why aging and pain intensity interfere with normal PA causing a deviation from the 'common area' in (M, B) space (Fig. 5). With decreasing physical capacity (impairment of physical functioning), longer resting periods are observed after activity periods resulting in decreased correlations (M) between successive *activity* and *rest* states.

While a number of studies have examined the PA in specific disorders, the quantification and modeling of the features of PA and the related behaviors remain challenging. We have shown that relevant information on the dynamics of human activity is embedded in the temporal pattern of occurrence of PA events. The data presented here is based on a large number of heterogeneous subjects (in terms of

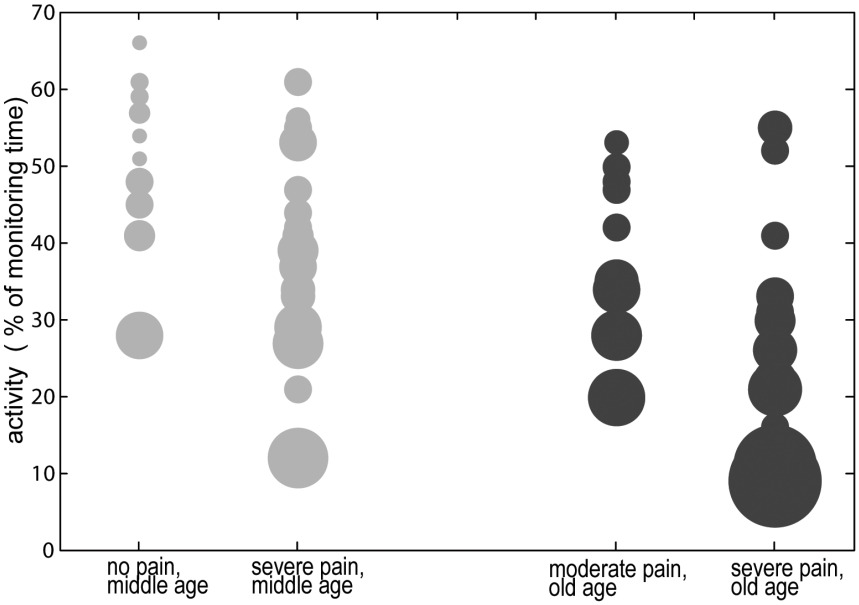

Figure 6 | Empirical evidence that different pain-behavioral models - defined as *fear-avoidance, endurance/over-activity* and *pacing* may characterize daily functioning in chronic pain patients. Each bubble contains subject's specific information about the cumulated *activity(%)* level (on the y-axis) and the statistical distance between distribution of *activity* and *rest* periods, A_{ar} (in the bubble relative size): *fear-avoidance* behavior might be attributed to the chronic pain patients with low *activity* levels while *endurance* might be attributed to the severe pain patients who perform high amounts of *activity* levels, comparable with no/moderate pain subjects. *Pacing* behavior might be associated to the chronic pain patients with high level of cumulated *activity* but with a more fragmented pattern and longer *rest* periods compared to *activity* periods (i.e. bigger bubble sizes, as observed for the patients in *the severe pain, middle age* group compared to the subjects in the *no pain, middle age group*).

Table 1 | Characteristics of each group (mean ± SD) and statistical differences between groups

	no pain, middle age (n = 14)	*severe pain, middle age* (n = 25)	Differences between groups	*moderate pain, old age* (n = 14)	*severe pain, old age* (n = 19)	Differences between groups
Pain intensity (VAS, 0 to 10)	0	7 ± 1.3	$p = 0$	3.6 ± 1.4	7.7 ± 1.3	$p \cong 0$
Age, yrs	57 ± 14	54 ± 9	$p = 0.63$	73 ± 10	74 ± 8	$p = 0.2$
Gender, n males (%)	8(53%)	15(60%)	$p = 0.32$	9(56%)	10(52%)	$p = 0.61$
Employed, n (%)	13(86%)	25(100%)	$p = 0.06$	2(0.13%)	0(0%)	$p = 0.1$
Diagnosis, n (type)	-	4(SS) 13(FBSS) 2(CRPS) 3(PVD) 1(LB) 1(PN) 1(HD)	-	5(SS) 3 (FBSS) 3(PVD) 1(LB) 1(Meralgya) 1(DA)	9(SS) 4(FBSS) 2(PVD) 1(PN) 1(DA) 2(HD)	-

Diagnosis: SS = spinal stenosis; FBSS = failed back surgery syndrome; CRPS = Complex regional pain syndrome; PVD = peripheral vascular disease; LB = low back and leg pain; PN = polyneuropathy; DA = deafferentation; HD = Herniated disc.

pain intensity, environment, age, etc.) in whom the bivariate Hawkes point processes is a convenient mathematical framework to model the dynamics of $a \rightarrow r$ and $r \rightarrow a$ transition times. The stochastic conditional intensity functions describing the time dependence of the transition rates (Methods, equation 1) provide a *'signature'* of the subjects' PA behavioral pattern through the set of parameters tuned to fit the experimental data (see Supplementary Figures S1–S72). Hawkes point processes have been used to model various human activities/social phenomena[39] including financial markets trading activity[40], online video views and conversation patterns[41]. In the context of PA patterns our results pave the way for further studies that might focus on the generalization to the *marked* case, by specifying for each $a \rightarrow r$ transition the movement intensity during the preceding *activity* period (e.g. in terms of walking duration, speed, body acceleration, or energy expenditure) and model in this way a process that convey more physically and pain/fatigue related information.

Finally, it is important to note that the findings of this study have inherent limitations related to the sample size and the data collection procedure. Due to the complexity and variety of human daily-life activities, the data collected from 72 subjects in the limited period of five days may be no sufficiently representative and therefore restrict the generalization of the results.

Methods

Study design and data collection. The analysis is performed retrospectively on data that were collected prospectively in an observational study designed to assess PA in chronic pain patients treated with spinal cord stimulation (SCS). The main inclusion criteria were eligibility for SCS therapy and pain-related limitation of the walking perimeter, therefore the group was not homogenous in terms of pathologies and demographic data (Table 1). The healthy pain free volunteers were recruited from patients' relatives or the medical staff of the pain clinic. After approval of the local ethical committee, and written informed consent was obtained, PA was monitored under normal unrestricted life conditions using three miniaturized data-loggers (55 × 40 × 18 mm, 50 g) stuck to the skin with medical adhesive patches. The data-loggers included inertial sensors (accelerometers and gyroscopes), memory, electronics for the data acquisition and rechargeable batteries. One device was fixed on the chest (sternum) to measure the trunk vertical and frontal accelerations, and the angular velocity in the sagittal plane. Two devices were fixed on one leg (thigh and shank) aligned with the medio-lateral axis to measure vertical and frontal accelerations and the angular velocity of the thigh and of the shank in the sagittal plane. This sensor configuration allows accurate detection (sensitivity and specificity superior to 95%) of body postures (sitting, standing, lying) and walking activity[24]. The subjects were instructed to install the devices and start the recording in the morning before engaging in daily activities. Chronic pain conditions were assessed using the usual pain intensity experienced by subjects during PA monitoring period. The subjects were asked to rate their pain on a visual analog scale (VAS) from 0 to 10.

Estimation of burstiness and memory. *Short-term correlations* are estimated with the 1st order serial correlation/memory coefficient M defined for the sequence of successive *activity-rest* periods (pattern '*ar*') (Fig. 1a) as follows[30]:

$$M = \frac{1}{n-1}\sum_{i=1}^{n-1}\frac{(ar_i - m_1)(ar_{i+1} - m_2)}{\sigma_1\sigma_2}$$

where n is the number of *activity* and *rest* periods, $m_1(m_2)$ and $\sigma_1(\sigma_2)$ are the mean and standard deviation of $ar_i(ar_{i+1})$ respectively ($j = 1,\ldots,n-1$). *Burstiness/variability* is estimated with the coefficient[30]:

$$B = \frac{\sigma_{ar} - m_{ar}}{\sigma_{ar} + m_{ar}}$$

where m_{ar} and σ_{ar} are the mean and standard deviation of the pattern '*ar*'.

Estimation of multi-scale burstiness using the Fano factor. In order to provide a stable/robust estimate of parameters, the PA event series of each subject are obtained by concatenating the data from the five consecutive days. Thus, the occurrence time of events are mapped onto $(0,T_n)$, as follows: if t is the time of an event occurring in the d^{th} day ($d = 1,2,\ldots,5$) then the occurrence time of this event in the final PA event series is $t + \sum_{i=1}^{d-1} l_i$, where l_d is the length of d^{th} day and T_n is the total monitoring time during the five days.

The Fano factor is defined as the ratio of the variance of the number of transitions to the mean number of transitions in time windows of specified length, T:

$$F(T) = \frac{\text{var}(N_k(T))}{mean(N_k(T))}$$

where $N_k(T)$ is the number of transitions in k^{th} window of length T (Fig. 1c). For a data block of length T_n, the window length T is progressively increased from a minimum of 2 sec to a maximum of $T_n/10$ so that at least ten non-overlapping windows are used to estimate $F(T)$. If transitions ($a \rightarrow r$ and $r \rightarrow a$) are organized in temporal clusters/bursts (and bursts within bursts), the Fano factor varies as $F(T) \propto T^{\omega_F}$ for long counting times. The exponent ω_F is bounded in the range $0 \le \omega_F \le 1$, increasing values toward the upper bound providing a measure of the correlations and burstiness of transitions over various time scales. If transitions are randomly distributed then $F(T)$ is flat for all time scales and $\omega_F \approx 0$[7,31].

Modelisation of PA pattern using the bivariate Hawkes point processes. Within the framework of this process the temporal behavior (time-dependence) of $r \rightarrow a$ and $a \rightarrow r$ sequences is modeled by the *conditional intensities* $\lambda_a(t|H_t)$ and $\lambda_r(t|H_t)$, respectively, which represent the infinitesimal rate at which transitions are expected to occur around a particular time t, conditional of the recent history of the transitions sequences up to time t, $H_t = \left\{t_i^a \cup t_j^r : t_i^a, t_j^r < t\right\}$:

$$\begin{aligned}\lambda_a(t|H_t) &= \mu_a + \sum_{t_i^a < t}\alpha_a e^{-\beta_a(t-t_i^a)} + \sum_{t_j^r < t}\alpha_{ar} e^{-\beta_a(t-t_j^r)} \\ \lambda_r(t|H_t) &= \mu_r + \sum_{t_j^r < t}\alpha_r e^{-\beta_r(t-t_j^r)} + \sum_{t_i^a < t}\alpha_{ra} e^{-\beta_r(t-t_i^a)}\end{aligned} \quad (1)$$

where μ_a, μ_r are background rates of spontaneous transitions (i.e. not related to the timing of the other transitions) and β_a, β_r are the rates of decay controlling the influence of the time distance to past transitions on overall rates λ_a, λ_r. The scale parameters α_a and $\alpha_r$measure the impact of an $r \rightarrow a/a \rightarrow r$ transition on the rate of subsequent $r \rightarrow a/a \rightarrow r$ transitions (self-dependence) while α_{ar} and α_{ra} measure the impact of an $a \rightarrow r/r \rightarrow a$ transition on the rate of subsequent $r \rightarrow a/a \rightarrow r$ transitions (mutual-dependence). As each transition occurs, the conditional rate increases according to the values of the scale parameters (Fig. 1d). More specifically, an $r \rightarrow a/a \rightarrow r$ transition occurring at the basal rate μ may trigger a burst/cluster of successive transitions. The expected cluster sizes c_a and c_r are equal with the total integrated intensity of the exponential kernels[33]:

$$\begin{aligned}c_a &= 1\Big/1 - \left(\int_0^\infty \alpha_a e^{-\beta_a t}dt + \int_0^\infty \alpha_{ar} e^{-\beta_a t}dt\right) = 1\Big/1 - \left(\frac{\alpha_a}{\beta_a} + \frac{\alpha_{ar}}{\beta_a}\right) \\ c_r &= 1\Big/1 - \left(\int_0^\infty \alpha_r e^{-\beta_r t}dt + \int_0^\infty \alpha_{ra} e^{-\beta_r t}dt\right) = 1\Big/1 - \left(\frac{\alpha_r}{\beta_r} + \frac{\alpha_{ra}}{\beta_r}\right)\end{aligned} \quad (2)$$

and the average of the occurrence rate of transitions is given by:

$\hat{\lambda}_a = E[\lambda_a(t|H_t)] = \mu_a c_a$ and $\hat{\lambda}_r = E[\lambda_r(t|H_t)] = \mu_r c_r$. Given the parametric form of the bivariate process in eq. 1, the set of parameters are estimated using the maximum likelihood estimation (MLE). The log-likelihood can be computed as the sum of the likelihood of each process:

$$L^{ar}(\mu_a,\mu_r,\beta_a,\beta_r,\alpha_a,\alpha_{ar},\alpha_r,\alpha_{ra}) = L^a(\mu_a,\beta_a,\alpha_a,\alpha_{ar}) + L^r(\mu_r,\beta_r,\alpha_r,\alpha_{ra}) \quad (3)$$

$$\begin{aligned} L^a = &\sum_{i=2}^{n} \log(\mu_a + \alpha_a R_a(i) + \alpha_{ar} R_{ar}(i)) - \mu_a T_n + \frac{\alpha_a}{\beta_a}\sum_{i=1}^{n}(e^{-\beta_a(T_n - t_i^a)} - 1) + \\ &\frac{\alpha_{ar}}{\beta_a}\sum_{j=1}^{m}(e^{-\beta_a(T_n - t_j^r)} - 1) \\ L^r = &\sum_{j=2}^{m} \log(\mu_a + \alpha_r R_r(j) + \alpha_{ra} R_{ra}(j)) - \mu_r T_n + \frac{\alpha_{ra}}{\beta_r}\sum_{i=1}^{n}(e^{-\beta_r(T_n - t_i^a)} - 1) + \\ &\frac{\alpha_r}{\beta_r}\sum_{j=1}^{m}(e^{-\beta_r(T_n - t_j^r)} - 1) \end{aligned} \quad (4)$$

where R are recursive expressions given by:

$$R_a(1) = R_{ar}(1) = R_r(1) = R_{ra}(1) = 0 \quad (5)$$

$$R_a(i) = e^{-\beta_a(t_i^a - t_{i-1}^a)}(1 + R_a(i-1)) \quad (6)$$

$$R_{ar}(i) = e^{-\beta_a(t_i^a - t_{i-1}^a)}(R_{ar}(i-1)) + \sum_{\{j: t_{i-1}^a \le t_j^r < t_i^a\}} e^{-\beta_a(t_i^a - t_j^r)} \quad (7)$$

$$R_r(j) = e^{-\beta_r(t_j^r - t_{j-1}^r)}(1 + R_r(j-1)) \quad (8)$$

$$R_{ra}(j) = e^{-\beta_r(t_j^r - t_{j-1}^r)}(R_{ra}(j-1)) + \sum_{\{i: t_{j-1}^r \le t_i^a < t_j^r\}} e^{-\beta_r(t_j^r - t_i^a)} \quad (9)$$

The MLE of the vector parameter $\theta = (\mu_a,\mu_r,\beta_a,\beta_r,\alpha_a,\alpha_{ar},\alpha_r,\alpha_{ra})$ is given by $\hat{\theta} = Arg\min_{\theta}(L^a(\theta) + L^r(\theta))$ subject to positivity and stability constraints, $\beta_a,\beta_r,\alpha_a,\alpha_{ar},\alpha_r,\alpha_{ra} > 0$ and $\frac{\alpha_a}{\beta_a}, \frac{\alpha_{ar}}{\beta_a}, \frac{\alpha_r}{\beta_r}, \frac{\alpha_{ra}}{\beta_r} < 1$ respectively. The MLE is performed using the *simulated annealing* optimization method and the goodness of fit for the data of each subject is assessed using the *QQ*-plot and the Kolmogorov-Smirnov plot (*KS*-plot) (*see* Supplementary Method S3).

Statistical analysis. PA parameters are calculated for each subject, then the mean and standard deviation values are calculated for each group of subjects. The distribution of parameters in each group is tested for Normality (Shapiro-Wilk test), and based on Normality test the differences between groups is assessed using two-sided Student's t-test or nonparametric Mann-Whitney test. Correlations between different PA parameters are quantified using Spearman rank-correlation test.

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Author contributions

A.P.I., E.B., K.A. designed the study and wrote the paper. A.P.I. contributed methodological tools and analyzed the data.

Additional information

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