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Application of principal component analysis in clinical gait research: identification of systematic differences between healthy and medial knee-osteoarthritic gait.

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Abstract (246 of 250 words)

For a successful completion of a movement task the motor control system has to observe a multitude of internal constraints that govern the coordination of its segments. The purpose of this study was to apply principal component (PC) analysis to detect differences in the segmental coordination between healthy subjects and patients with medial knee osteoarthritis (OA). It was hypothesized that (1) systematic differences in patterns of whole body movement would be identifiable with this method even in small sample sized groups and that (2) these differences will include compensatory movements in the OA patients in both the lower and upper body segments. Marker positions and ground reaction forces of three gait trials of 5 healthy and 5 OA participants with full body marker sets were analyzed using a principal component analysis. Group differences in the PC-scores were determined for the first 10 PC-vectors and a linear combination of those PC-vectors where differences were found defined a discriminant vector. Projecting the original trials onto this discriminant vector yielded significant group differences ($t(d=8)=3.011$; $p=0.017$) with greater upper body movement in patients with knee OA that was correlated with the medial-lateral ground reaction force. These results help to characterize the adaptation of whole-body gait patterns to knee OA in a relatively small population and may provide an improved basis for the development of interventions to modify knee load. The PC-based motion analysis offered a highly sensitive approach to identify characteristic whole body patterns of movement associated with pathological gait.

Introduction

Clinical gait analysis has for many years contributed to the understanding of the etiology of gait abnormalities, aided in treatment decisions, and allowed for evaluation of the treatment efficacy (Davis, 1997). Standard procedure in today's gait analysis is the quantification of joint angles and, through inverse dynamic calculations, resultant joint forces and moments. Differences in gait patterns between different populations or due to an intervention or disease are commonly identified by statistically analyzing maximum or minimum values from these variables individually. An important shortcoming of the standard motion analysis approach is that it singles out and statistically analyzes individual variables, thereby treating them as independent and overlooking the fact that all kinematic or kinetic variables characterizing aspects of the same movement are interdependent. It is perhaps not surprising, given the limited view of traditional analysis methods, that the understanding of how and why individuals adapt to injuries, disease or different interventions is often still not clear.

A substantial challenge for the identification of differences in gait patterns is caused by the large inter- and intra-subject variability observed in any movement (Bernstein, 1967; Winter, 1984; Bartlett et al., 2007; Stergiou et al., 2006). Studies aiming at identifying systematic differences in gait patterns typically tackle variability issues by normalizing the data, e.g. to body height or body weight, averaging over multiple trials, or by including large sample sizes in order to reach the threshold of statistical significance. However, the variability stems not only from anthropometric differences between subjects or different strategies of executing a movement, but also from the fact that human movement is a multi-segmental motion (multi-body system) with many degrees of freedom that create a high-dimensional space of potential solutions for the same movement task (Bernstein, 1967).

The many degrees of freedom described by Bernstein (1967) allow for a large variability in any single variable, however, the coordination between different body segments necessary for

the execution of any movement requires the observation of a multitude of internal and external constraints that have to be observed by the motor control system for the task to be successful. For example, upright standing is possible with many different knee angles – almost straight leg or deeply crouched – but for any given knee angle, the ankle and hip angles can no longer be arbitrarily chosen without compromising the success of the task. Hence, large variability is possible in the original variables knee angle, ankle angle and hip angle, however, the tolerance for deviations from the constraints defining how these angles correlate is small, making the actual solution space much tighter (circles in Figure 1). Interventions or systematic difference between different populations change the set of constraints defining how individual joints interrelate (triangles in Figure 1). Quantifying if and how the interrelationship between movement variables changes due to a clinical condition or due to an intervention, offers a set of information that has often been overlooked, and that may be more sensitive than the single-value statistical analysis applied in conventional biomechanical studies.

Performing a principal component analysis (PCA) identifies correlations between observed variables and thus offers one technique to identify group differences in a movement's solution spaces within the space of degrees of freedoms that were experimentally determined. PCA has already been successfully applied in several studies identifying subtle differences between movement patterns (Boyer et al., 2012a; Maurer et al., 2012; Nigg et al., 2012; Astephen and Deluzio, 2005; Troje, 2002; Witte et al., 2010; Nigg, 2010). The current study combined all waveforms of the marker coordinates and the ground reaction forces (GRF) and thus operated in a vector space that combined all directly measured gait variables. The postulated high sensitivity of the PCA-based gait analysis may not only facilitate identification of subtle differences that were not detectable with conventional methods, it may also allow detecting systematic differences in groups of much smaller sample size. This property would be very useful in many clinical applications, for example, when investigating rare pathologies (Kim

and Fung, 2011), specific manifestations of underlying constructs (e.g. stroke), or individual responses to treatment interventions.

To demonstrate the applicability of the PCA-based gait analysis technique for research into small sample sized groups, this study explored differences between patients suffering from medial knee osteoarthritis (OA) and matched healthy reference subjects. Such differences have been identified in previous studies relying on larger sample sizes. Specifically, more extended knee at touchdown of the injured leg (Huang et al., 2008; Mündermann et al., 2005; Landry et al., 2007) and throughout stance phase (Deluzio and Astephen, 2007; Astephen et al., 2008) as well as increased lateral GRF and vertical GRF load rates shortly after touchdown (Mündermann et al., 2005) have been reported for OA patients. Differences in joint moments (Astephen et al., 2008; Mündermann et al., 2005; Landry et al., 2007) were not investigated in our study, however, changes in pelvis and shoulder movements have been proposed as explanation for the reported differences in joint moments (Mündermann et al., 2005) and increased trunk sway has also been suggested as a mechanism to reduce joint loading (Mündermann et al., 2005; Hunt et al., 2008; Mündermann et al., 2008). Differences in upper body kinematics identified by the PCA as applied in the current study are interdepend and therefore, if they exist, are directly correlated to the alteration in lower body motion and GRFs.

In summary, the first aim of this study was to test the feasibility of applying a PCA-based gait analysis approach to studies of small sample sizes. It was hypothesized that known systematic differences in gait kinematics and in ground reaction forces between knee OA patients and healthy reference subjects would be detectable even in small sample sized groups. Second, it was hypothesized that changes in shoulder and pelvis motion predicted in previous studies will appear as part of the systematic differences between OA patients and healthy volunteers.

Methods

Participants

This study analyzed gait data recorded for a single-blind washout, double-blind treatment, double dummy cross-over design study investigating the effect of two pain treatments on gait of knee osteoarthritis patients (Boyer et al., 2012b). After a rigorous screening procedure this study included six patients with medial knee OA of Kellgren-Lawrence radiographic severity grades 2 or 3 who completed all measurements. Five of them suffered from arthritis in the right knee and formed the patient group (61.6 ± 2.1 yrs; 178.1 ± 5.3 cm; 88.5 ± 7.5 kg) in our study. Five age and gender matched healthy volunteers (61.0 ± 2.6 yrs; 174.2 ± 3.7 cm; 79.1 ± 7.3 kg) selected from a database at Stanford University formed a control group. All subjects had provided informed written consent, and had agreed to their data being used in future research projects not directly linked to the study they originally participated in.

Measurement procedures and instrumentation

Three trials from the placebo phase for each subject walking at self-selected, fast-paced speed (“catching a bus”) on an 11 m long walkway were selected for this analysis. Kinematic data and 3D-ground reaction forces were recorded for one step. Kinematic data were collected at 120 Hz sampling frequency with an 8-camera motion analysis system (Qualysis, Gothenburg, Sweden) using 36 reflective markers. The markers were positioned according to a previously described point-cluster technique (Andriacchi et al., 1998), which uses a redundant set of markers on the thigh and shank of the injured leg. In addition, 3D-ground reaction force (GRF) data were recorded at 120 Hz sampling frequency using a multi-component force-plate (Bertec Corporation, Columbus, Ohio, USA).

Data analysis

All calculations and statistical procedures were carried out in Matlab® (The MathWorks Inc., Natic, MA, USA). Three normalization steps were conducted to prepare the data for the

principal component analysis. First, all marker coordinates were expressed in coordinates relative to the horizontal position of the pelvis, i.e. the horizontal center of the four pelvis markers was subtracted from all marker coordinates. Second, kinematic and GRF data were temporally normalized in relation to the step cycle by interpolating each marker or GRF coordinate waveform using a piecewise cubic hermite interpolating polynomial. The stance phase of the injured leg from touchdown (0%) to take off (100%) and the last and first parts of the swing phase corresponding to 20% of the stance period were selected for analysis (in total -20% to 120% of the stance phase). The waveforms of all variables (marker coordinates and GRF) were then resampled to 112 time points, with 80 points representing the stance phase and 16 points representing the end and beginning of the swing phase of the injured leg. Third, the influence of anthropometric differences between subjects on the variability of the variables was minimized by calculating and subtracting for each coordinate the mean over the analyzed period and then normalizing the waveform amplitude to unit standard deviation.

The resultant normalized waveforms of all variables were concatenated into one data vector V with 12432 vector components ([36 markers + GRF] x 3D coordinates x 112 time points for each waveform). Performing a PCA on the matrix formed from the data vectors of all 30 trials [(5 OA subjects + 5 control subjects) * 3 trials] yielded (a) principle component vectors ($\mathbf{PC_i}$) indicating the direction of the largest variation in the dataset; (b) eigenvalues (EV_i) indicating the amount of variation in the data explained by a given $\mathbf{PC_i}$; and (c) scores, c_i, obtained by projecting individual trials onto the $\mathbf{PC_i}$. Each $\mathbf{PC_i}$ represents a characteristic manner of how individual trials deviated from the average gait pattern. Characteristic differences between the gait patterns of the OA patients and the healthy controls were identified by comparing the scores c_i of the first 10 $\mathbf{PC_i}$. Thereto, mean scores were first calculated for the 3 trials of each subject. These mean scores were then compared between the groups using the effect size *Cohen's d* (Table 1). A discriminant vector **D** calculated as a weighted linear combination of those $\mathbf{PC_i}$ that

yielded large effect sizes ($d_i > 0.8$;(Cohen, 1992), Table 1) combined the characteristic deviations from the mean gait patterns that are associated with differences between the test groups. The weight factors used in this linear combination were the eigenvalues EV_i:

$$\boldsymbol{D} = \sum_i \delta_i \, EV_i \, \boldsymbol{PC_i} \quad with \quad \delta_i = \begin{cases} 1 & for \;\; d_i > 0.8 \qquad (Table\ 1) \\ 0 & for \;\; 0.8 > d_i > -0.8 \;\; (Table\ 1) \\ -1 & for \;\; d_i < -0.8 \qquad (Table\ 1) \end{cases}$$

The trial vectors were then projected onto the discriminant vector and mean scores calculated for each subject. A Student's T-test (independent samples) based on these mean scores was used to test if the gait features characterized by the discriminant vector were significantly different in the two test groups.

Visualization of gait features that differed between the test groups

Since the calculation was based on the marker positions, it was possible to visualize the characteristic differences between the healthy and pathologic gait patterns by arbitrarily selecting the normalized data of one healthy subject (black circles in Figure 2), adding the discriminant vector, and then retracing the normalization steps (red circles in Figure 2). Differences between the gait patterns turned out to be subtle and were therefore exaggerated for the visualization by multiplying the discriminant vector with an amplification factor of 10. Characteristic group differences in the GRF were similarly visualized by arbitrarily selecting the GRF of one healthy subject as reference curves (black lines in Figure 3) and then adding the systematic deviations from the mean that were characteristic for the difference between healthy and OA group (red lines in Figure 3).

Results

A discriminant vector combining PC_1, PC_8, and PC_9 incorporated characteristic differences between movement patterns of the OA and of the matched control group. These

differences were significant (t(d=8)=3.011; p=0.017) within the two groups of only 5 subjects. The three **principal** components that constituted the discriminant vector explained together 26.2% of the variance observed in the walking patterns between different trials (Table 1).

The differences in the movement patterns between OA and controls were interpreted by examining the visualization of the discriminant vector (Figure 2). Characteristic features of the differences between the gait of the healthy and the OA group in the sagittal plane (Figure 2, top) included: (a) the OA patients showed signs of limping: the contralateral leg was longer weight bearing at the end of its stance phase and earlier weight bearing at its beginning; (b) increased knee extension at touchdown and throughout stance phase, which is accompanied by corresponding changes in ankle and hip angles; and (c) increased hip and knee flexion of the contralateral leg in swing phase.

Characteristic features visible in the frontal plane (Figure 2, bottom) were (d) greater knee adduction in early to mid-stance and subtle increase of knee abduction in late stance; (e) differences in pelvis motion in late stance and during push-off from the injured leg; (f) increased sway of upper trunk and shoulders; (g) a shift of the contralateral foot position at touch-down and take-off which might either be related to the limping seen in the sagittal plane or it may be a sign of increased lateral pelvis motion (due to the normalization procedure this would only be visible indirectly, i.e. in the foot position).

Characteristic group differences in the GRF between the healthy and the OA group were also observed in the medial-lateral and vertical force component, but no noteworthy differences were found in the anterior-posterior force components (Figure 3, top). In the medial-lateral force component (Figure 3, middle) a tendency towards a higher initial force peak (A in Figure 3) and a reduced force peak in the second half of the stance phase (B) were observed. The vertical GRF component (Figure 3, bottom) showed differences in the loading rate characteristics after touchdown (C) and higher forces at mid-stance (D).

Discussion

The results of this study supported the hypothesis that systematic differences between knee OA and healthy gait can be identified even in small-sized test groups when using PCA as a mathematical tool that analyzes the interrelation between variables. This suggests that this approach to the analysis of clinical gait data may open the doors for other research areas where it is impossible to recruit a large sample sizes.

This study did not only confirm observations of previous studies with respect to OA gait characteristics by identifying differences in lower body motion and in external forces (Figure 2, items a, b, g; Figure 3 A, C), it also showed that changes in shoulder and pelvis motion (Figure 2, item f) are part of the systematic differences between OA and healthy gait. The methods described here had the capacity to detect quantitative evidence in a relative small sample that one of the mechanisms to alter force profiles at the arthritic knee joint is related to the coordination of upper and lower body motions. This result is consistent with observation made in larger studies (Mündermann et al 2005). In fact, there are only two mechanisms that can produce changes in the resultant forces and moments acting in a joint: changes in the joint loading resulting from altered upper body movement characteristics or changes in the alignment of the joint itself. The subtle, yet systematic difference in the knee adduction characteristics observed in this study (Figure 2 item d) is evidence of a second mechanism that is also relevant for understanding changes in the OA knee mechanics. This may be an indication of an altered knee joint alignment or stability affecting the knee kinematics. The observation of a change in both the upper and lower body coordinated pattern of movement in relation to the changes in GRF suggests a mechanism in OA patient gait for the reduction of both the first and second peak external knee adduction moments previously observed in similar cohorts (Mündermann et al., 2005; Deluzio and Astephen, 2007). This information provides an improved understanding of

the natural adaptation mechanisms that knee-OA patients use to unload their joint and prevent pain.

This study has provided unique insight into the characteristics of OA gait by linking Bernstein's degree of freedom model with modern techniques for biomechanical gait analysis. Bernstein stated that "coordination of movement is the process of mastering the redundant degrees of freedom" (Bernstein 1967) within the internal and external constraints imposed by the body and the environment. Our analysis is based on the assumption that a pathology or intervention changes some of these internal constraints and thus leads to an altered shape of the solution space of the movement task within the high-dimensional space spanned by Bernstein's degrees of freedom. By analyzing movement variability with a PCA we determine which of the constraints governing the interrelation between movement variables differ between the two test groups. In taking this perspective, our approach differs not only from traditional gait analysis, but also from previous studies that used PCA to identify differences in the waveforms of individual variables but did not combine several variables (Deluzio and Astephen, 2007; Astephen Wilson et al., 2011; Deluzio et al., 1997; Landry et al., 2007; Astephen et al., 2008; Brandon and Deluzio, 2011). Instead, this method is conceptually related to the idea that multi-muscle synergies (Kang et al., 2004; Latash et al., 2002; Latash, 2010; Bernstein, 1967) produce and control movement tasks and to theories such as the "uncontrolled manifold hypothesis" (Scholz and Schöner, 1999; Latash et al., 2007; Schoner, 1995) or the "optimal feedback control theory" (Todorov and Jordan, 2002; Todorov, 2004). Similar to our study, the "uncontrolled manifold hypothesis" analyses the solution space for a movement task, but focuses on identifying which variables affect the outcome of a task, i.e. variables that the motor control system has to monitor tightly, and which variables don't affect the outcome and thus shape an "uncontrolled manifold" within the solution space (Black et al., 2007). The "optimal feedback control theory" investigates how neuro-cerebral motor control processes influence

motion variability (Decker et al., 2012; Dingwell et al., 2010), while the current study focuses on how a clinical condition affects the internal and external constraints.

An important conceptual advantage of this method is that variability in the execution of a movement does not necessarily reduce the power of its statistical analysis. On the contrary, movement variability is necessary to reveal correlations between variables and thus leads to a clearer definition of the principal component axes and may even lead to higher statistical power when comparing PC-scores between groups. The high sensitivity to subtle but systematic differences in movement patterns that this approach has demonstrated in several previous studies (Boyer et al., 2012a; Maurer et al., 2012; Nigg et al., 2012; Astephen and Deluzio, 2005) and the applicability in studies with a small number of participants (as demonstrated here) are related to this conceptual advantage and are of great practical value.

This study choose to conduct the PCA with the original marker coordinates and the GRF data, not with secondary variables derived in further post-processing steps. The original marker coordinates represent all directly measured information without any pre-selection of variables (through the decision which secondary variables are calculated) or definition of arbitrary axes to define the motion of the joint and without the risk of introducing artifacts (Kristianslund et al., 2012). Furthermore, the marker coordinates facilitate the creation of stick figures to visualize the differences in the movement patterns (Figure 2; supplementary material) and thus promote a holistic viewpoint when interpreting the results. This approach has been used previously, not only for gait analysis (Federolf et al., 2012b; Daffertshofer et al., 2004; Troje, 2002; Eskofier et al., 2011) but also to investigate balance strategies (Federolf et al., 2012c) or more complex movements in sports (Federolf et al., 2012a).

An important limitation of any study relying on a small sample size is a potential sampling bias. This was minimized by selecting data from a study (Boyer et al., 2012b) where pre-defined, objective inclusion criteria had led to a small sample size despite a large pool of potential

volunteers. Limitations of the analysis approach include that PCA is a linear data analysis technique. It seems plausible that for small differences in the gait patterns a linearization is appropriate; however, this cannot be assumed in general. A second limitation is that a normalization of the dataset is necessary to reduce the influence of anthropometric differences on the results. In our experience, time normalization to percentage of stance phase (or step cycle), removal of each variable's mean, and normalization of each variable's amplitude to unit variance were – despite of the considerable loss of information – necessary steps to ensure that systematic differences could successfully be identified. However, this normalization levels out differences in the amplitude and therefore explains why the differences in the medial-lateral GRF peaks were not as pronounced as reported in previous studies (Mündermann et al., 2005).

Conclusions

This study applied a PCA-based movement analysis technique to clinical gait analysis. As opposed to classical gait analysis, which assesses differences in the amplitude of variables, this technique quantified differences in the coordination between variables. The technique detected systematic differences in gait characteristics between knee OA patients and healthy controls in small sample-sized groups and provided insight into the coordination of the lower and upper body segment motion and their relationship with external forces.

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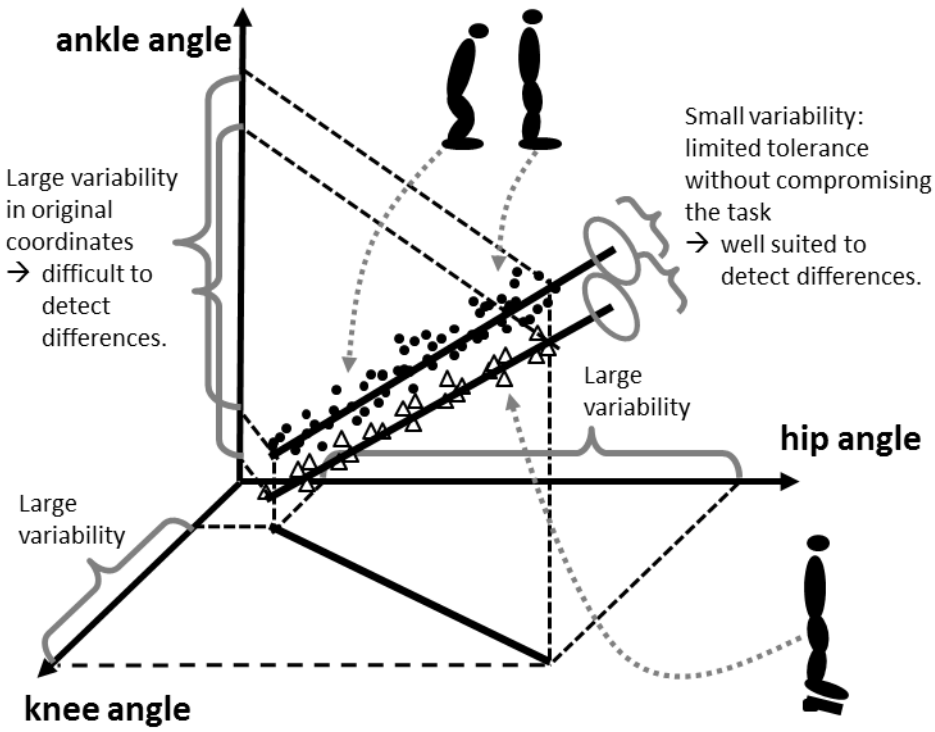


Figure 1: Schematic figure to visualize the internal constraints governing the interrelation between movement variables. The task “standing” can be accomplished with many different ankle, knee and hip angles leading to a large variability in these coordinates (filled circles). However, tolerance for deviations from how these angles correlate is small since such deviations would compromise the task. A pathology or intervention – here exemplified by standing on a shoe with elevated heel (hollow triangles) – alters not only the original movement variables but also how they interrelate. Detecting differences in such internal constraints therefore offers an alternative and potentially more sensitive approach for identifying systematic differences in a movement.

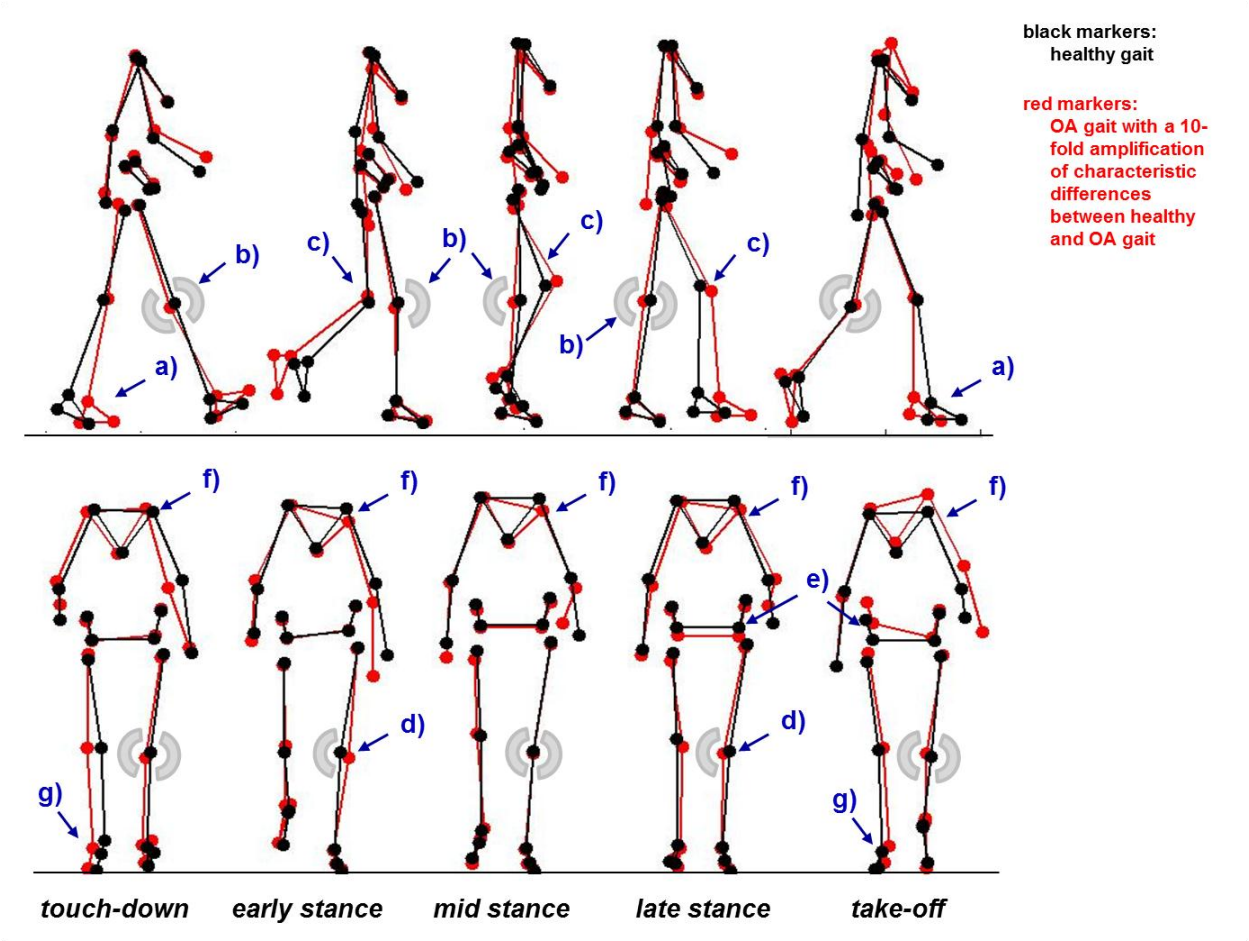
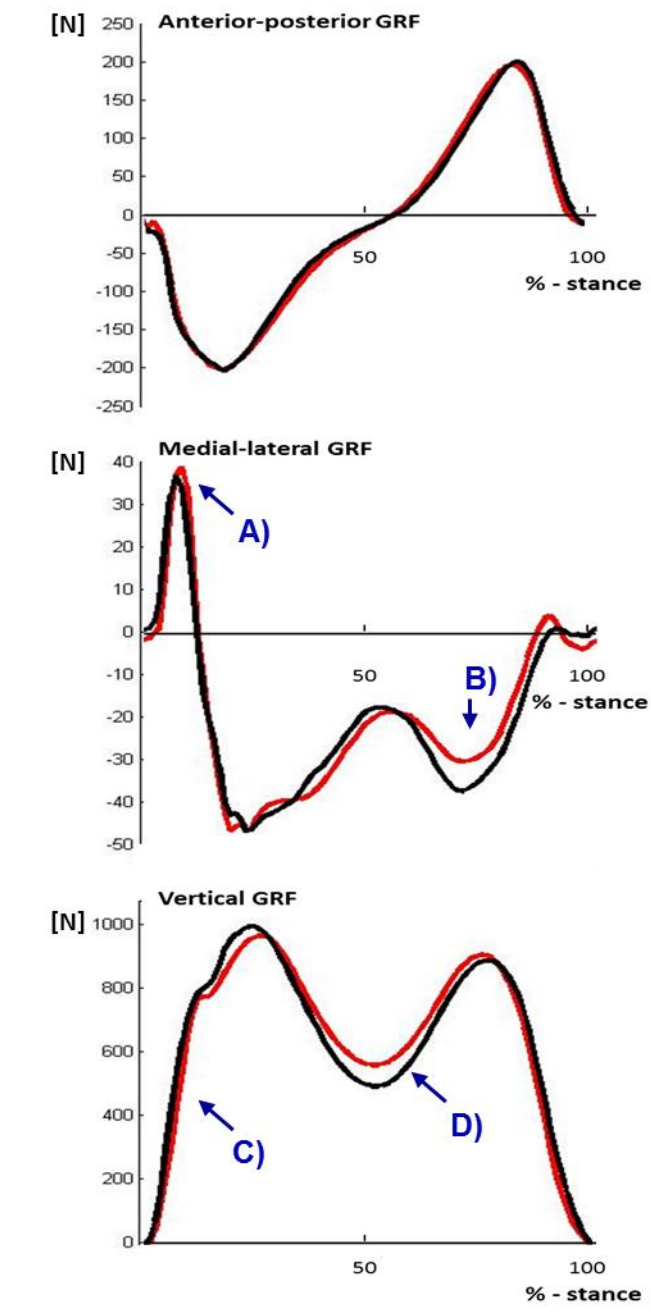


Figure 2: Stick figures representing postural differences in the stance phase of the injured leg (indicated by a grey circle). Deviations from the normal gait patterns due to knee OA were 10-fold amplified. Highlighted differences (a,b,c,d,e,f,g) refer to the items discussed in the text. For better clarity, only markers at the shoulders, sternum, elbows, wrists, iliac crests, ASIS, greater trochanter, knee, maleolus, calcaneus, and 5th metatarsal (21 of the 36 markers) were included in these figures.



Visualization of the group differences in the ground reaction forces (GRF). Black lines: healthy gait; red lines: OA gait. Highlighted differences (A,B,C,D) refer to the items discussed in the text. The differences in the shape of the GRF components were directly visible and were therefore not artificially amplified in this figure.