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Title Page

Title: Passive Intervertebral Motion Characteristics in Chronic Mid to Low Back Pain: a Multivariate Analysis.

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Passive Intervertebral Motion Characteristics in Chronic Mid to Low Back Pain: a Multivariate Analysis.

Key words

Multivariate analysis, low back pain, kinematics, motion analysis.

Introduction

Low back pain is now the leading cause of disability globally [1] . Despite this, approximately 90% of cases are of unknown origin (hence nonspecific low back pain - NSLBP) [2] . However, certain features of the spine are associated with an increased probability of back pain, such as Modic type 1 changes, disc extrusion, and spondylolysis [3] . These findings, and the typical mechanical symptoms of NSBLP, indicates that mechanical characteristics may play a part in back pain.

The spine, typical of the musculoskeletal system, operates with redundant degrees of freedom. Adequate motor control is therefore important in preventing buckling and stress concentrations [4] . Reeves et al. pointed to the importance of passive, as well as muscular restraints, in maintaining spinal performance and structural integrity [5] . Where the passive restraints are a function of the material properties of the discs, vertebral bodies and ligaments etc, which, while not actively used to control spine motion, can be seen as a slowly-changing control system that provides restraint in rate and range of movement.

Passive motion quantitative fluoroscopy (QF) is a method of measuring intervertebral (IV) motion in recumbent subjects, where trunk motion is induced by a motorised table [6–8]. Using QF, joint kinematics of a spinal region can be assessed throughout a motion cycle, providing information on its passive mechanical properties. This ability is important, given the putative role of the neutral zone in spinal stability, a region of IV motion around the neutral position, where little resistance to force is offered by the passive tissues [9] . QF has been found to have 'good' to 'excellent' reliability (ICC > 0.737) for range of motion (ROM) [10] , with errors of <0.7 degrees in an in-vitro study [7] .

Studies that have compared back pain populations to controls using QF support the hypothesis that characteristics of passive IV motion can discriminate back pain. Mellor et al, in a study of 40 chronic back pain sufferers and matched controls, found that groups differed on 'combined proportional range variances' (CPRV)[10] . This measure is based on the fact that individual IV joint's contribution to overall spinal bending varies over the course of the motion. CPRV is a measure of this variation, combined across all bending directions, and this study showed it was higher in patients. Breen and Breen found that chronic low back pain (LBP) patients had greater motion sharing inequality (MSI) between IV joints in a study comparing 20 patients with 20 matched controls [11] .

The high dimensionality of QF data (801 per motion in Mellor et al's study [10]) requires the selection of scalar variables of interest to make analysis tractable [12] . Hitherto, this selection has been based on *a priori* theoretical assumptions about which features are important. An alternative is to adopt a multivariate approach, in which the choice of features to analyse is based on objective criteria, and where between-groups differences can be made on the basis of the simultaneous

consideration of all chosen features, rather than a one-variable-at-a-time approach with its inherent weaknesses [13] . In this study, well-established linear multivariate methods were chosen for their relative simplicity and invertibility, which facilitates plotting and examining features in the original data space.

Previous studies, being based on the proportional contribution to total spinal angle, suffer from problems related to division by small numbers when the total spinal angle is small. Hence, approximately 20% of the data needs to be discarded near the neutral position. The present study avoids this problem by using IV angles directly [14,15] .

This study aims to obtain and describe the main dimensions of passive IV motion variations from passive QF data using principal components analysis (PCA). Using this lower dimensional description of the motion, assess if and how passive motion differs between back pain sufferers and controls.

Methods

Recruitment and Data Acquisition

This study is a re-analysis of data obtained from F Mellor's PhD study [16] . Recruitment, imaging protocol and initial processing of the images have been described in detail elsewhere [10,16] . In summary, 40 patients and 40 controls, matched for gender, age group (mean patients: 35.9, controls: 35.7), and BMI (mean patients: 24.5, controls: 24.5) were recruited and underwent passive motion QF.

Patients were otherwise healthy, aged 21-50, with low back pain lasting greater than three months. Their back pain was required to have mechanical aggravating and relieving factors, a Von Korff chronic pain grade II or higher [17] , a score of four or greater on the Roland Morris Disability questionnaire [18] , and positive prone instability tests [19] between L2 and L5.

Controls were those without back pain in the previous year, which had prevented normal activity for one day or more, and negative prone instability tests between L2–L5. Imaging protocol and preprocessing is listed below:

- Participants were asked to lie on a custom moveable table that rotated the lower half of the body with the axis of rotation placed at the L3/4 joint (see figure 1, used with permission [20]).
- For 'right' and 'left' motions, subjects were placed supine in the neutral position and rotated 40° to the right and left, each time returning to the neutral position.
- For 'flexion' and 'extension' motions, subjects were placed in a lateral recumbent position and the table was rotated 40° to flex and extend the spine, each time returning to the neutral position.
- Each motion (bending and return) took 12 seconds, and vertebrae L2 to L5 were imaged and analysed.
- Images were obtained at 15Hz using videofluoroscopy (Siemens Arcadis Avantic VC10A).

- Tracking templates were constructed manually to encompass each vertebral body in one frame. The templates were then registered to vertebral positions in other frames using a cross-correlation similarity measure to obtain relative vertebral body orientations [21] . IV angles for each IV joint were obtained from differences between adjacent vertebral body orientations.

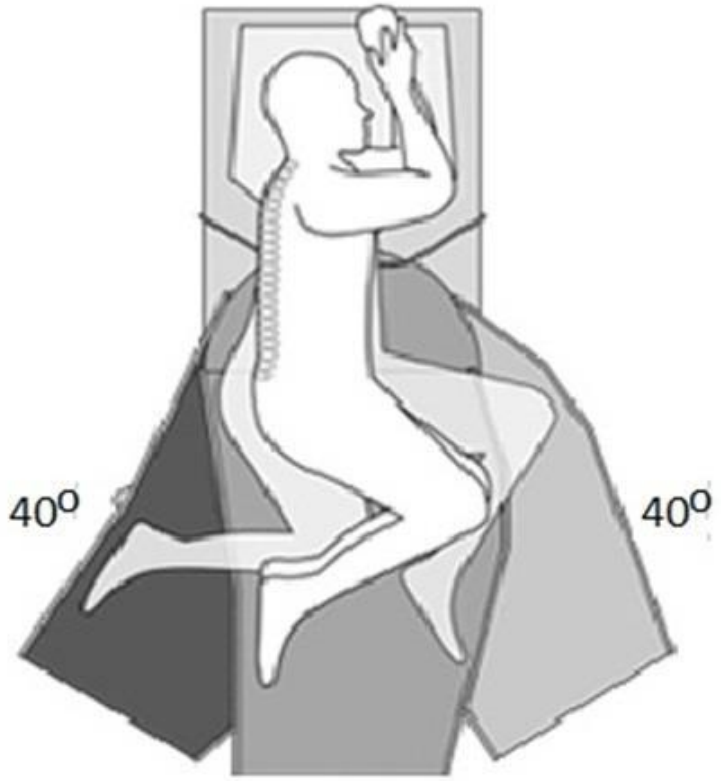

Figure 1: Diagram of passive motion table for sagittal plane motion.

For each motion direction ('left', 'right', 'flexion', 'extension'), 801 IV angles were obtained. In some cases there were missing data at the extremity of each motion. To address these gaps, to smooth the data, and to reduce the number of data points, this study divided the data into two halves: from neutral to end of range, and end of range to neutral. Each half was separately fitted to a smoothing spline, whose smoothing parameters were chosen using generalised cross-validation (GCV)[22] . GCV is based on a random, zero mean, serially uncorrelated model for the noise, and seeks to estimate a smoothing parameter just sufficient to eliminate this noise, but preserving as much of the signal as possible. Using the fitted spline, data were resampled to 40 points per half and the two haves were rejoined. 40 points were chosen as this far exceeds the expected number of PC dimensions of interest. Numbers of points in excess of the numbers of participants results in PC dimensions with zero eigenvalues, which would not be retained in further analyses.

Data Analysis

The resulting sequences of angles, one for each direction, were analysed using PCA. The aim of PCA is to describe the data more efficiently by using a new (often much smaller) set of variables called principal components (PCs). The underlying assumption behind PCA, and other dimension reduction methods, is that the data resides in a lower dimensional space than the space of the observed variables. For example, imagine points within a three dimensional space, where the points all lie in a plane. Each are represented by three coordinates, but one of these coordinates is, in a sense redundant, given that all points lie in a plane. This redundancy is reflected in correlations between the coordinates. PCA exploits correlations in the data in order to estimate the dimensionality of the underlying space in which the data resides (see figure 2). Observations, however, are often contaminated with noise, which are usually uncorrelated. PCs are ordered according to how much variance in the data they explain (indicated by their eigenvalues), which can be plotted on a 'scree plot' (see figure 3). The choice of how many PCs to retain was aided by observing inflection points in the scree plots [23] , and by using the broken stick method [13] . Both of these methods estimate the underlying dimensionality of the data by identifying PCs whose eigenvalues are greater than what would be expected from observing pure uncorrelated noise. Each PC represents different features of motion, which require interpretation, with each subject having different weightings on these (PC scores), depending on how these features are represented in subject's motions. These PCs were plotted in the original data space of IV angles to aid interpretation, i.e. PC scores where converted back into angles and plotted (see figure 4, for an example).

Using the retained PCs, differences between back pain and control groups were tested for each motion using the Hotelling T2 test, a multivariate equivalent of the Student's t-test [24] . This test relies on the assumption of multivariate normality, so a distribution-free permutation test was used in addition[25] to guard against violations of this assumption.

To determine how groups differed, linear discriminant analysis (LDA) was carried out. LDA calculates a linear combination of input variables which best discriminates two groups, based on maximising the ratio of between and within group sum of squares, termed the linear discriminant (LD), with each subject having a score placing them on this scale (the LD score) [26] . LD scores were visualised by plotting them in the original space of IV angles to aid interpretation of group differences (see figure 2).

LD scores were used to predict which group each subject belonged to. The quality of this prediction was assessed with leave-one-out cross-validation. In this, an LDA model is calculated on the remaining data after one subject's data is removed. This model is used to calculate an LD score for the left out subject, from which a prediction of class membership is made. The proportion of correctly classified subjects was used as a measure of quality of the LDA classifier. To see how sensitive the results were to the choice of number of retained PCs, a variable number of PCs (1-10) were used in the cross-validations.

LDA is somewhat restrictive in specifying that scores are a linear function of the input variables. Quadratic discriminant analysis (QDA) is more flexible in allowing quadratic terms in this function. QDA was used to assess whether more complex non-linear dimension reduction methods are needed, which would be indicated by a significantly better classification performance in QDA over LDA.

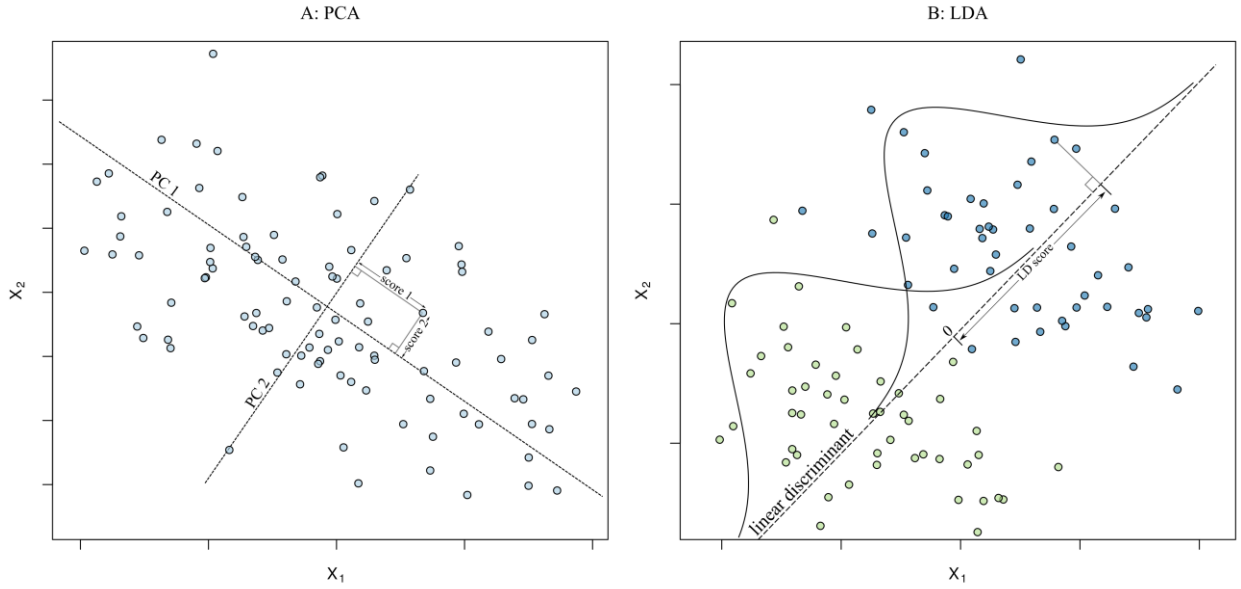

Figure 2: Geometrical interpretation of PCA and LDA, showing how input variables (X_1 & X_2) become PC and LD 'scores'. ***Graph A*** *- PCA. PC 1 is a straight line whose direction is chosen to maximise the variance of orthogonal projections of data on to it. The point at which a data point projects onto the PC gives its score for that PC. PC 2 is similarly defined, subject to it being orthogonal to PC 1. In high dimensional cases, less important PCs (i.e. those explaining less variance) are dropped to provide a more succinct representation of the data.* ***Graph B*** *- LDA. Here there are group labels (green and blue data). A straight line (the 'linear discriminant') is obtained whose direction maximises the group difference of the orthogonal projections of data onto it. The position of the projection of a data point on to the line is called its LD score.*

Results

PCA Results

Estimation of the number of PCs to retain gave similar results for the broken stick method and scree plot examination, both indicating that three PCs should be retained for all motion directions (see figure 3 for flexion, see link to data repository for others). For all motions, ~95% of the variance is explained by 5-6 PCs.

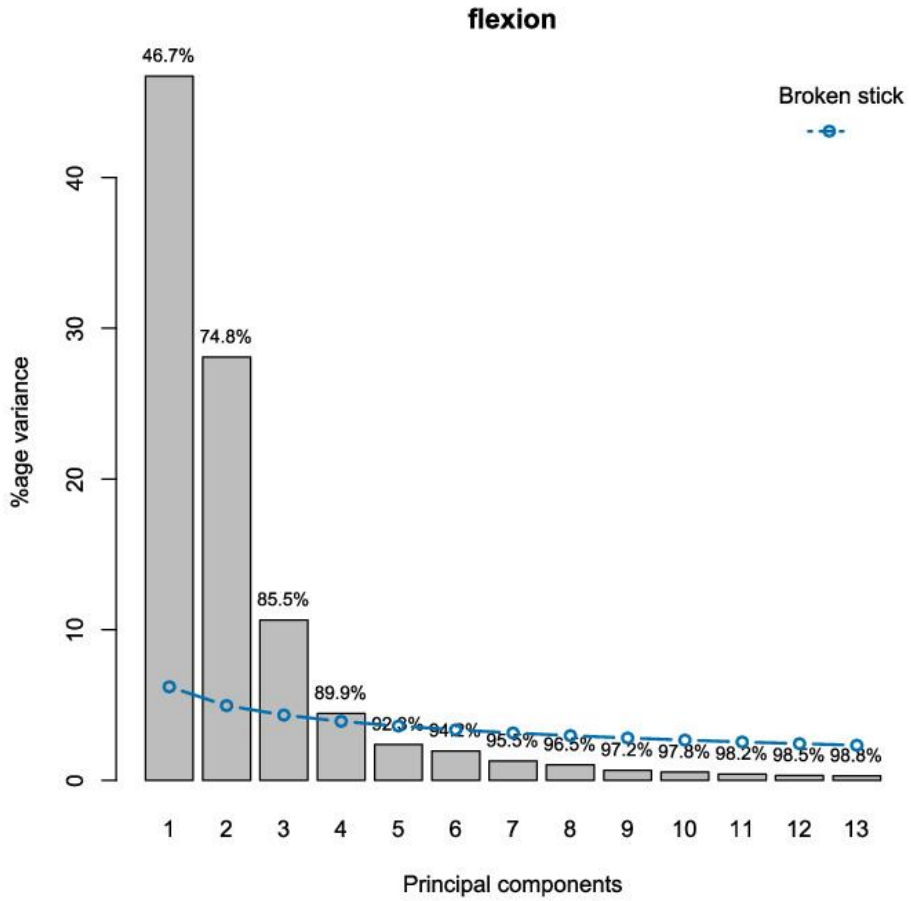

Figure 3: Screeplot for flexion motion. Broken stick model and 'knee' of plot indicate three PCs should be retained, by distinguishing PCs whose eigenvalues are greater than what would be expected from observing uncorrelated noise.

Plotting and interpreting each PC pointed to similar patterns across all four motions. The first PC represented mainly a variation in ROM across all joints, in which motion is distributed evenly between joints (see figure 4 for flexion, see link to data repository for others). Positive PC scores represent above-average ROM, negative scores represent below-average ROM. The second (figure 5) and third (not shown) PCs represented mainly variation in the distribution of motion between joints. In PC 2, positive scores correspond to above average ROM at L4/5 but less than average ROM at the other joints. For PCs greater than 3, the variations captured represent mainly different 'shapes' in the motion curve. That is, PCs 1-3 represent variation in joint ROM, but with similar patterns of acceleration/deceleration, whereas PCs > 3 represent variations in acceleration/deceleration beyond that due to a variation in ROM. (see figure 6 for example). The one exception to this pattern was extension, where ROM variation was correlated with some degree of variation in shape of the motion curve (see figure 7).

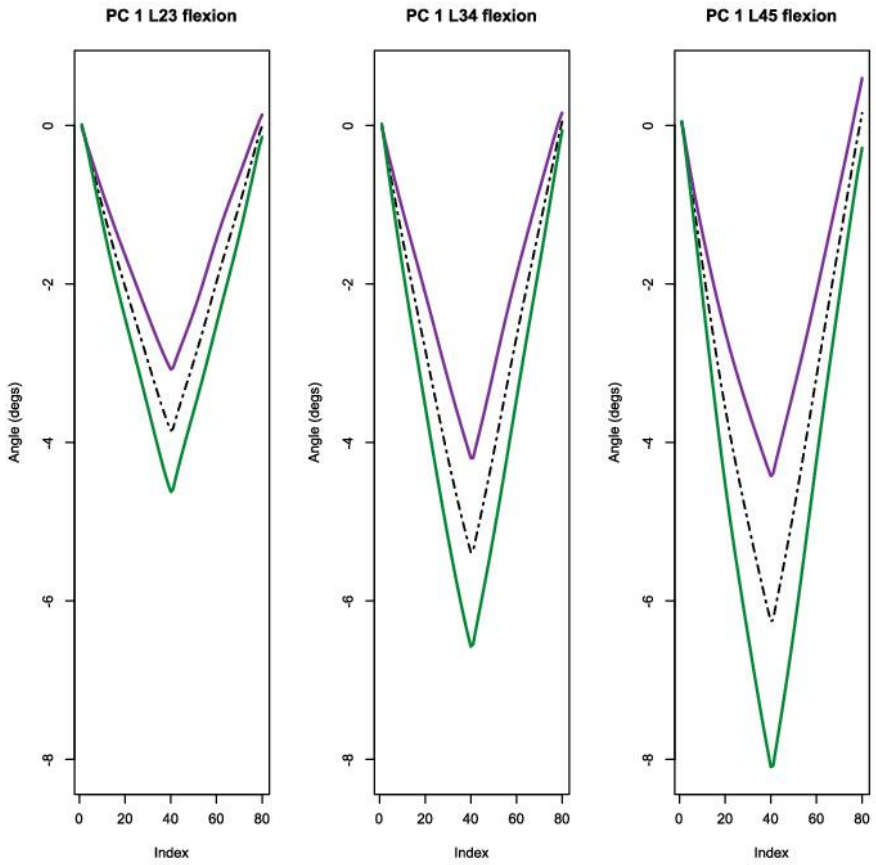

Figure 4: PC 1 flexion. This shows the main way IV motion varies across the sample. This mode of variation can be interpreted as variation in uniform ROM across all joints. Mean motion: black dotted line, +1 s.d.: green solid line, -1 s.d.: purple solid line. The data index is used as a surrogate for table motion on the horizontal axis.

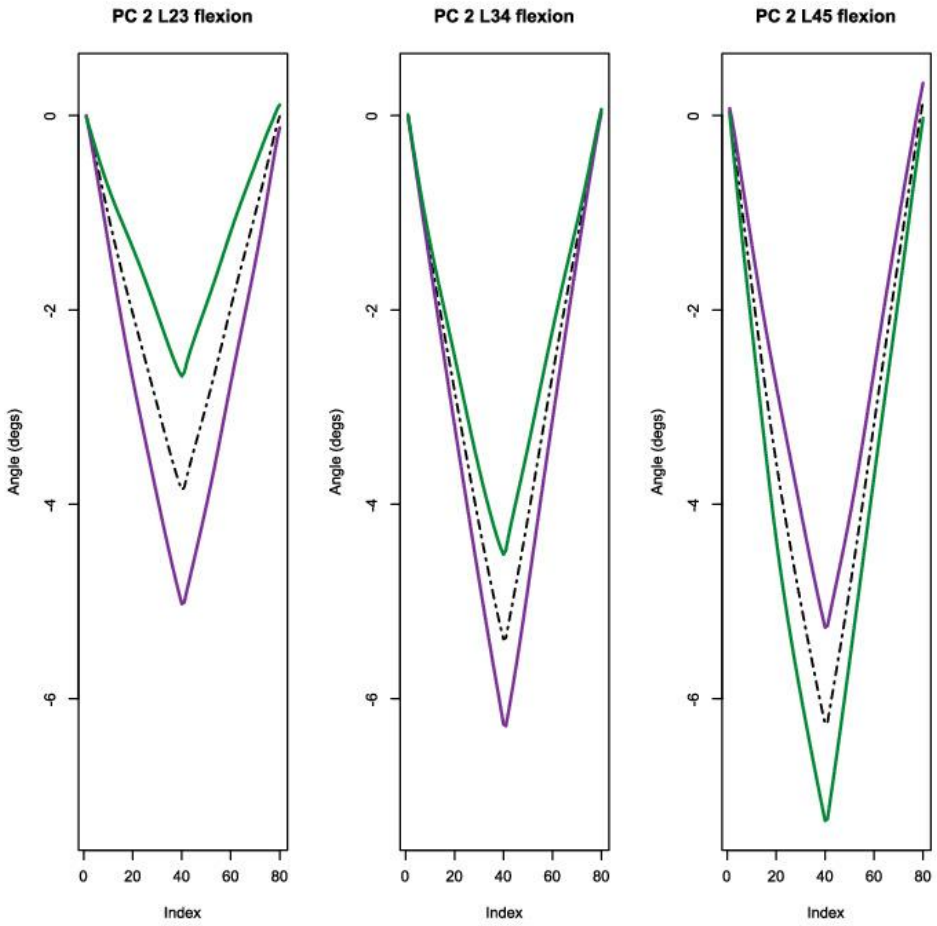

Figure 5: PC 2 for flexion motion, showing remaining main mode of variation, after having accounted for PC 1 variation. For positive scores (green), ROM is greater than average at L4/5, whilst it is less than average at other joints. Mean: black dotted line, green solid line: +1 s.d., purple solid line: -1 s.d. The data index is used as a surrogate for table motion on the horizontal axis.

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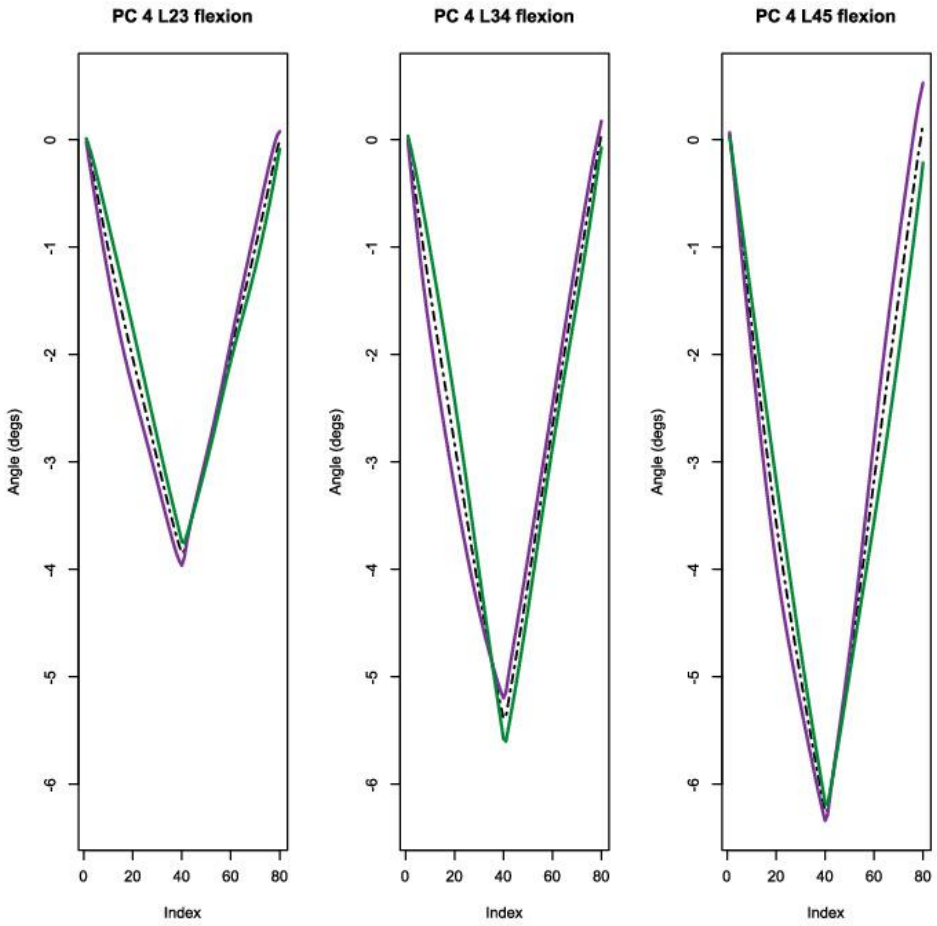

Figure 6: PC 4 for flexion motion. Main feature is variation in the shape of the motion curve, e.g. increased angular velocity (greater negative gradient) of the purple curve during the first part of the motion. Mean: black, green: +1.5 s.d., purple: -1.5 s.d.. The data index is used as a surrogate for table motion on the horizontal axis.

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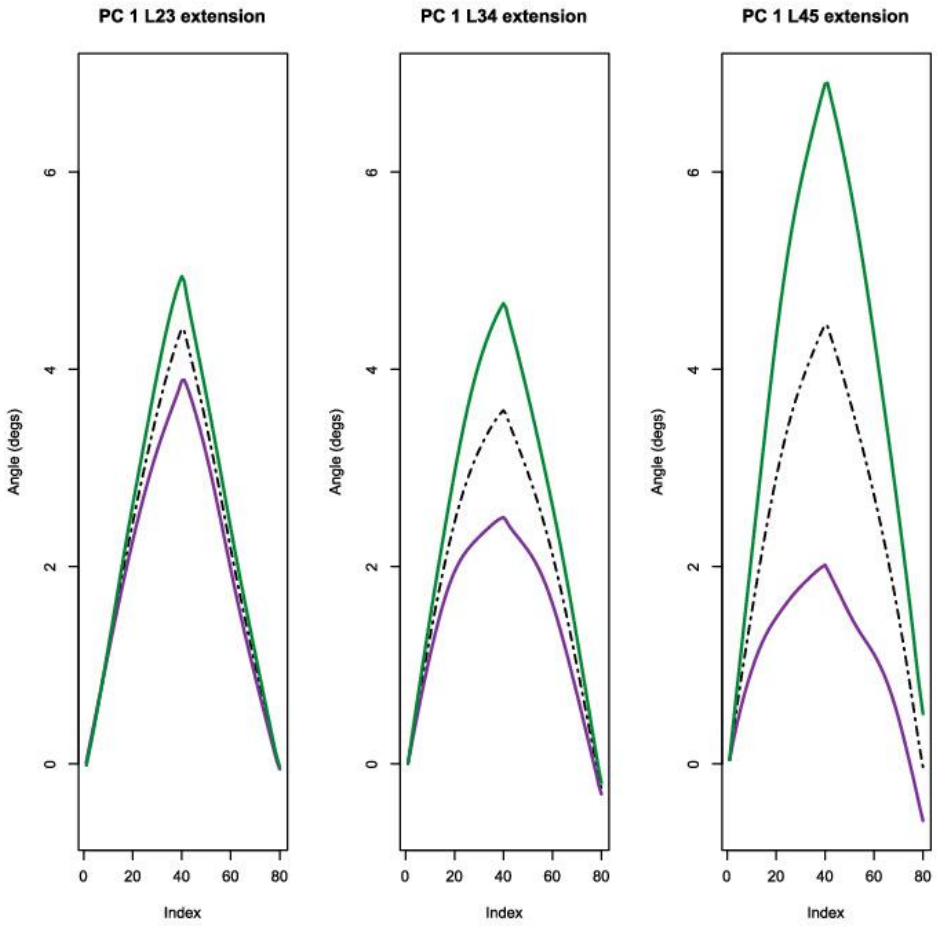

Figure 7: PC 1 extension. Variation in ROM is correlated with some variation in the shape of the motion curve, seen mainly at L4/5, where negative scores are associated with a flattening of the peak & asymmetry. Mean: black, green: +1 s.d., purple: -1 s.d. The data index is used as a surrogate for table motion on the horizontal axis.

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187 Representing motion using the first three PC scores, a Hotelling T-squared and a permutation test
188 were used to compare groups. This showed a significant difference between groups for coronal
189 plane motions only ('right': T2 = 10.62, p = 0.02 and 'left': T2 = 9.67, p=0.03). The permutation test
190 gave the same p-values as the Hotelling T-squared test.

191 *LDA and QDA Results*

192 The performance of LDA and QDA as predictors of back pain status for the coronal motion
193 directions are shown in figure 8, relative to the number of PCs used to represent motions. For
194 sagittal plane motions (extension and flexion), neither LDA nor QDA achieved statistically
195 significant classification accuracy (not shown – see supplementary material). For coronal plane
196 motions (‘right’ & ‘left’) groups were variably distinguishable, depending on the number of PCs
197 used to represent motion. There was no clear advantage of using QDA over LDA, although there is
198 a marginal improvement when using QDA for the ‘right’ motion. Separability does not appear to
199 increase with the number of PCs used, with no more than 4 PCs sufficing (first two for ‘left’, first
200 four for ‘right’).

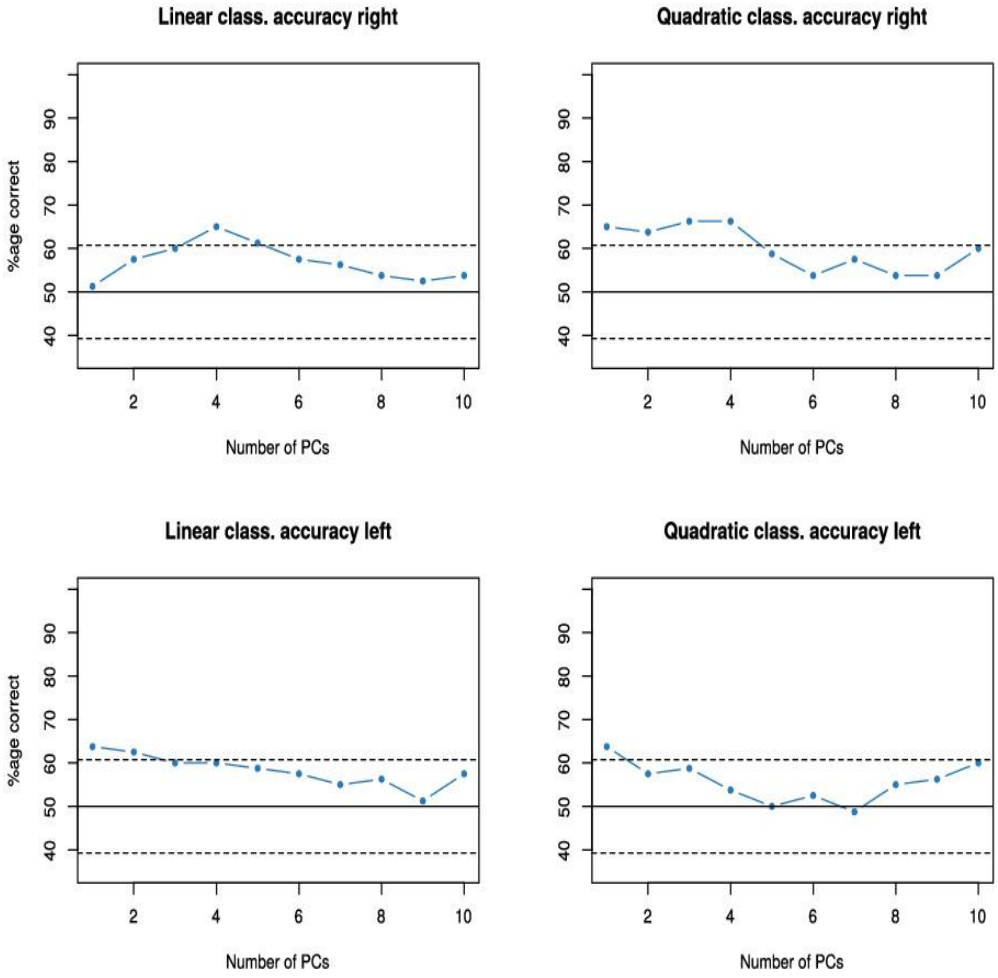

Figure 8: Prediction accuracy (percentage correctly classified) for coronal plane motions using leave-one-out cross-validation versus number of input PCs. Linear (left) and quadratic (right) discriminant analysis. Dotted horizontal lines show the H_0 rejection region; points outside these dotted lines achieve statistical significance at the 0.05 level.

201

202 LD scores were plotted and interpreted for coronal plane motions only, as sagittal plane motions
203 showed no significant differences (see, instead, see link to data repository). The 'left' motion
204 showed that the control group had a greater ROM at L4/5, but smaller ROM at L2/3 and L3/4
205 (figure 9). For the 'right' motion, there is greater ROM at L4/5 for the controls, but a lower ROM at
206 L3/4. There is also a difference in shape of the motion curve for this motion, although this might be
207 due to the presence of an outlier (figure 10),

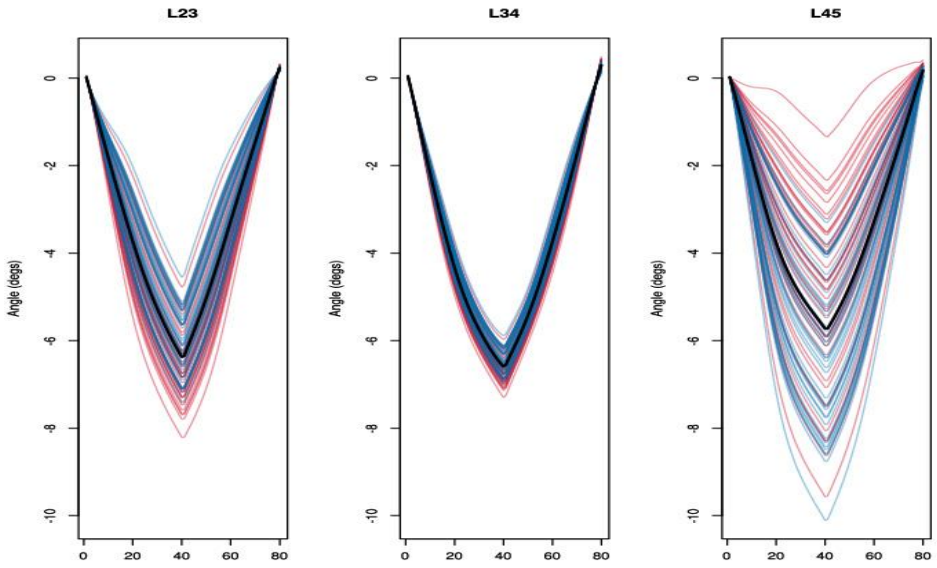

Figure 9: Projection of data onto linear discriminant of the LDA model using the first 2 PCs, 'left' motion. This shows the features by which the two groups differ maximally. The control group (blue) has a smaller ROM at L2/3 and L4/5, but greater ROM at L4/5 than the back pain group (red). The data index is used as a surrogate for table motion on the horizontal axis.

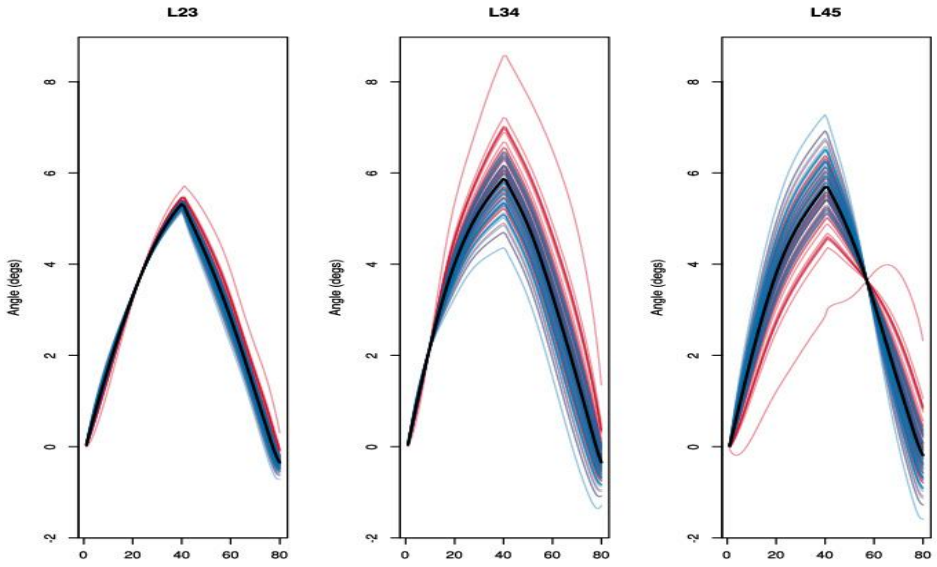

Figure 10: Projection of data onto linear discriminant of LDA model using the first 4 PCs as input, 'right' motion. This shows the features by which the two groups differ maximally. The control group (blue) has a smaller ROM at L3/4, but greater ROM at L4/5. There also appears to be differences in shape of the motion curve, due to differences in angular velocity (gradients) at different points in the motion. There is an extreme value visible in the L4/5 motion curves which may be skewing the results. The data index is used as a surrogate for table motion on the horizontal axis.

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Discussion

PCA identified three main modes of variation for passive IV motion. PC 1 was associated with uniform variation in ROM across the whole of this spinal region. PCs 2 & 3 were associated with variations in how ROM was shared within the spinal region. In these first three modes, there was little shape variation, with curves resembling that of the mean, which had a simple, smooth and symmetrical shape. The one exception was extension, where reduced ROM correlated with peak flattening and asymmetry. The nature of this association of shape change with ROM is unclear, but may indicate that relatively stiff spines exhibit hysteresis in lower lumbar joints, leading to asymmetry between outward and return movements.

Statistically significant differences in passive IV motion between NSLBP subjects and matched controls were found for coronal plane motions only, using low dimensional PC representations. LDA indicated there was reduced motion ROM at the most caudal joint in NSLBP participants, compensated for by higher ROM in the more cranial joints. In both cases, differences related largely to ROM and its distribution between joints, and little to the shape of the motion curve. Studies of distribution of motion between IV joints for flexion of the lumbar spine in healthy people indicate a gradual decrease of ROM from caudal to cranial, which they term the 'spine rhythm' [27] . If this finding can be translated to coronal plane motion, it would support the idea that increased motion in the cranial joints is deviation from normal.

The relative lack of motion curve shape variation appearing in the first few PCs may be because shape varies on an individual basis, and not in a consistent pattern across the sample. Examining the individual motion curves demonstrates wide variation in shape (see link to data repository), which shows that this mode of variation cannot be reduced to a few dimensions, at least not with PCA. Theoretically, an expanded neutral zone might cause a difference in shape of motion curve between groups [28] . However, this effect maybe obscured by the mechanical properties of adjacent joints. For example, an increased neutral zone would alter the leverage exerted on neighbouring joints. This altered stress applied to adjacent joints would be expected to confound the observation of their stress-strain curves, and may explain why the neutral zone is more important in in-vitro studies of intervertebral mechanics [10] .

These results are similar to studies that have shown that motion sharing inequality can distinguish back pain subjects from controls, in so far as both point to alteration in how motion is distributed between IV joints [11,29] . An inequality or alteration in restraint may predispose to mechanical back pain through a greater tendency to buckle. The spine, without active muscular control, has been shown to buckle with axial loads far less than typical in-vivo axial loads [30] . It could be speculated that alterations in motion sharing in the spine over the lifetime of an individual, due to degenerative changes or alterations in soft-tissue mechanical properties, may undermine the dynamic stability of its coordination patterns, an important consideration in the motor control of redundant systems, such as the spine [31,32] . It has been shown that motion sharing inequality correlates with age and degenerative changes [11] .

The reason why only coronal plane motions distinguished groups may be due to lower mean lumbar ROM for coronal plane active motions [33] . Presumably, the greater force required to obtain the same ROM during imposed passive motions may highlight the effect of differences in passive restraints. In addition, greater accuracy for tracking vertebral bodies in coronal plane motions may

mean these measurements are less contaminated with noise. Breen et al found that RMS error in IV angles obtained by vertebral tracking from videofluoroscopy images was 0.32 degrees for coronal plane and 0.52 degrees for sagittal plane motions [7] . The smoothing of the motion data due to spline interpolation should reduce the noise, but may not have been entirely successful, especially if the noise was not random and serially uncorrelated.

A limitation of the method used in this study is that it was limited to consideration in only two planes. Assessing dynamic motion in the transverse plane would require dynamic 3D imaging, which is not possible with 2D videofluoroscopy. There is some evidence of altered distribution of ROM in axial rotation between spinal segments being associated with back pain [34] .

This study undertook the first multivariate analysis of continuous passive IV motion data in a matched sample of back pain sufferers and controls, confirming the importance of altered passive restraints between vertebrae. Back pain is an enduring mystery, but in recent decades expanding the scope from just considering tissue pathology to incorporating psychosocial mechanisms, has led to deeper insights into this condition. Between these two lies the study of low-level control of intersegmental coordination, which may offer a better understanding of symptom variation over shorter time scales, which often are associate with variation in motion and posture. It may also help explain why NSLBP often remits and relapses without apparent reason [35] . Future longitudinal studies should focus on the time course of alterations in intersegmental coordination, to understand how they relate to the time course of NSLBP.

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Ethical approval: Not required

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