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

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Abstract: Purpose
Studies comparing back pain patients and controls on continuous intervertebral kinematics have shown differences using univariate parameters. Hitherto, multivariate approaches have not been applied to this high dimensional data, risking clinically relevant features being undetected. A multivariate re-analysis was carried out to estimate main modes of variation, and explore group differences.
Methods
40 participants with mechanical back pain and 40 matched controls underwent passive recumbent quantitative videofluoroscopy. Intervertebral angles of L2/3 to L4/5 were obtained for right and left side-bending, extension, and flexion. Principal components analysis (PCA) was used to identify the main modes of variation, and to obtain a lower dimensional representation for comparing groups. Linear discriminant analysis (LDA) was used to identify how groups differed.
Results
PCA identified three main modes of variation, all relating to range of motion (ROM) and its distribution between joints. Significant differences were found for coronal plane motions only (right: p=0.02, left: p=0.03) . LDA identified a shift in ROM to more cranial joints in the back pain group.
Conclusion
The results confirm altered motion sharing between intervertebral joints in back pain, and provides more details about this. Further work is required to establish how these findings lead to pain, and so strengthen the theoretical basis for treatment and management of this condition.

Cover Letter

Kevin Brownhill PhD
University College of Osteopathy
275 Borough High Street, London, SE1 1JE

23 March 2020

Dear Dr Black,

We wish to submit an original research article entitled "*Passive Intervertebral Motion Characteristics in Chronic Mid to Low Back Pain: a Multivariate Analysis*" for consideration by Medical Engineering & Physics.

We confirm that this work is original and has not been published elsewhere, nor is it currently under consideration for publication elsewhere.

In this paper, we report on a multivariate re-analysis of inter-vertebral kinematics. This is significant because this is a complex dataset and bias may be introduced through over-reliance on a limited set of univariate parameters.

We believe that this manuscript is appropriate for publication by Medical Engineering & Physics because it employs an imaging, biomechanical and statistical approach to the problem of back pain. We believe this multidisciplinary approach is very appropriate to your journal.

Back pain is a difficult problem, and understanding its causes requires objective biomarkers. Passive motion videofluoroscopy is one such tool , which has shown promise. However, there is a need to check previous findings using a more sophisticated analytic approach.

We have no conflicts of interest to disclose.

Please address all correspondence concerning this manuscript to me at kevin.brownhill@uco.ac.uk

Thank you for your consideration of this manuscript.

Sincerely,

Kevin Brownhill

***Declaration form**

Journal: MEDICAL ENGINEERING & PHYSICS

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

Declarations

The following additional information is required for submission. Please note that this form runs over two pages and failure to respond to these questions/statements will mean your submission will be returned to you. **If you have nothing to declare in any of these categories then this should be stated.**

Conflict of interest
All authors must disclose any financial and personal relationships with other people or organisations that could inappropriately influence (bias) their work. Examples of potential conflicts of interest include employment, consultancies, stock ownership, honoraria, paid expert testimony, patent applications/registrations, and grants or other funding.

Conflicts of Interest

There are no conflicts of interest

Please state any sources of funding for your research

No funding source obtained

Ethical Approval

Work on human beings that is submitted to *Medical Engineering & Physics* should comply with the principles laid down in the Declaration of Helsinki; Recommendations guiding physicians in biomedical research involving human subjects. Adopted by the 18th World Medical Assembly, Helsinki, Finland, June 1964, amended by the 29th World Medical Assembly, Tokyo, Japan, October 1975, the 35th World Medical Assembly, Venice, Italy, October 1983, and the 41st World Medical Assembly, Hong Kong, September 1989. You should include information as to whether the work has been approved by the appropriate ethical committees related to the institution(s) in which it was performed and that subjects gave informed consent to the work.

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The original study from which data for this re-analysis was obtained was granted ethical approval by:
the UK National Research Ethics Committee
Southampton A (09/H0502/99)

This re-analysis did not seek ethical approval

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If you have no declaration to make please insert the following statements into your manuscript:

Competing interests: None declared

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***Referee Suggestions**

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Highlights

- A multivariate analysis of continuous motion passive inter-vertebral joint kinematic data was carried out
- Significant differences between low back pain participants and controls was found for coronal plane motions only
- Differences found indicated a compensatory shift of motion to the upper lumbar spine in patients.

Title Page

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

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Abstract

Purpose: Studies comparing back pain patients and controls on continuous intervertebral kinematics have shown differences using univariate parameters. Hitherto, multivariate approaches have not

been applied to this high dimensional data, risking clinically relevant features being undetected. A multivariate re-analysis was carried out to estimate main modes of variation, and explore group differences.

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Results: PCA identified three main modes of variation, all relating to range of motion (ROM) and its distribution between joints. Significant differences were found for coronal plane motions only (right: $p=0.02$, left: $p=0.03$) . LDA identified a shift in ROM to more cranial joints in the back pain group.

Conclusion: The results confirm altered motion sharing between intervertebral joints in back pain, and provides more details about this. Further work is required to establish how these findings lead to pain, and so strengthen the theoretical basis for treatment and management of this condition.

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 its aetiology.

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 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 passive 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 is a measure of variability of IV joint's proportional contribution to overall spinal motion; being 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 requires the selection of scalar variables of interest to make analysis tractable. 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 [12] . 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 [13, 14] .

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 [15] . Recruitment, imaging protocol and initial processing of the images have been described in detail elsewhere [10, 15] . In summary, 40 patients and 40 controls, matched for gender, age group, and BMI 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 [16] , a score of four or greater on the Roland Morris Disability questionnaire [17] , and positive prone instability tests[18] 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.
- 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. The templates were then registered to vertebral positions in other frames using a cross-correlation similarity measure. IV angles were calculated from the change in rotation of the templates between image frames.

For each motion direction (‘left’, ‘right’, ‘flexion’, ‘extension’), tracking sequences were sampled to match the control table motion, 40 degrees bending and return, at 0.1 degree intervals. From this 801 discreet data points were obtained describing the IV angles of each vertebral body pair 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 a cross-validation technique [19] . Using the fitted spline, data were resampled to 40 points per half and the two haves were rejoined.

Data Analysis

The resulting sets of angles, one for each direction, were analysed using PCA. PCA creates a new set of variables, termed principle components (PCs), each being a linear combination of the original data. PCs are uncorrelated with each other, and are ordered according to how much variance in the data they explain. By retaining only the first few PCs, the number of variables required to explain variation in the data is reduced. The retained PCs were then used for further analysis. The choice of how many PCs to retain was aided by observing inflection points in the scree plots [20] , and by using the broken stick method [12] (see figure). Each PC represents different features of motion,

133 with each subject having different weightings on these (PC scores), depending on how these
134 features are represented in subject's motions. These PCs were plotted in the original data space of
135 IV angles to aid interpretation.

136 Using the retained PCs, differences between back pain and control groups were tested for each
137 motion using the Hotelling T2 test, a multivariate equivalent of the Student's t-test [21] . This test
138 relies on the assumption of multivariate normality, so a distribution-free permutation test was used
139 in addition[22] to guard against violations of this assumption.

140 To determine how groups differed, linear discriminant analysis (LDA) was carried out. LDA
141 calculates a linear combination of input variables which best discriminates two groups, based on
142 maximising the ratio of between and within group sum of squares, termed the linear discriminant
143 (LD), with each subject having a score placing them on this scale (the LD score) [23] . LD scores
144 were visualised by plotting them in the original space of IV angles to aid interpretation of group
145 differences.

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

153 LDA is somewhat restrictive in specifying that scores are a linear function of the input variables.
154 Quadratic discriminant analysis (QDA) is more flexible in allowing quadratic terms in this function.
155 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.

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 for flexion, see supplementary materials for others). For all motions, ~95% of the variance is explained by 5-6 PCs.

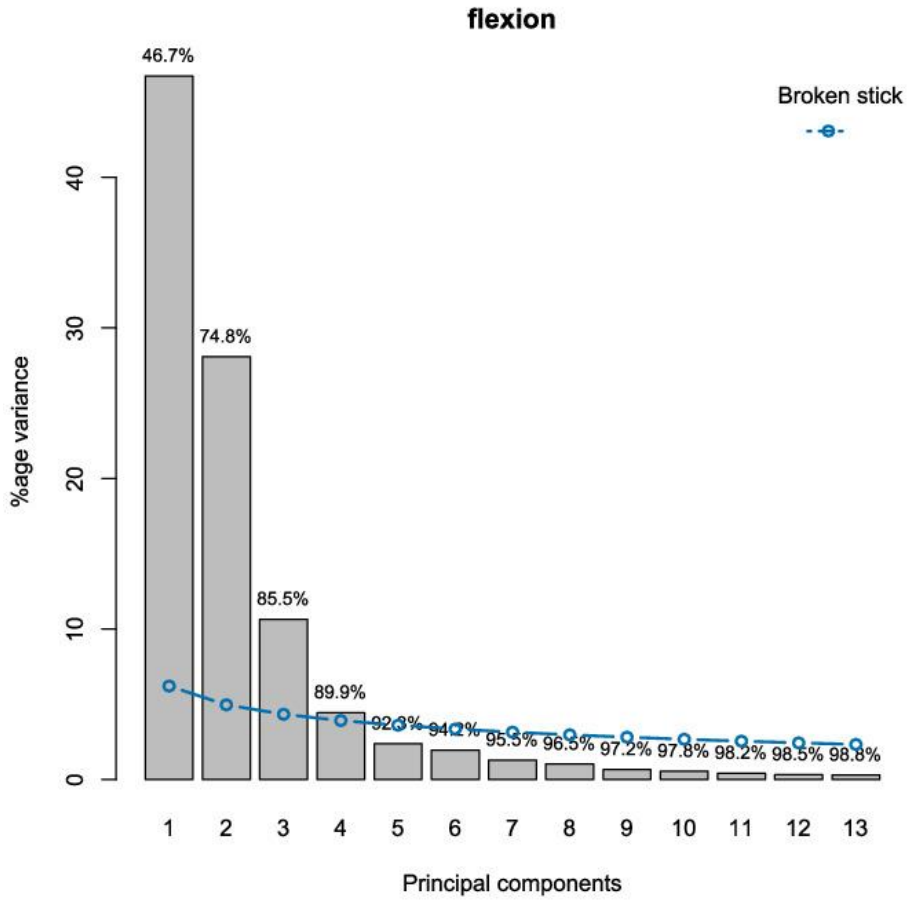

Figure 1: Screeplot for flexion motion. Broken stick model and 'knee' of plot indicate three PCs should be retained.

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 for flexion, see supplementary materials for others). Positive PC scores represent above-average ROM, negative scores represent below-average ROM. The second (figure) 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 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).

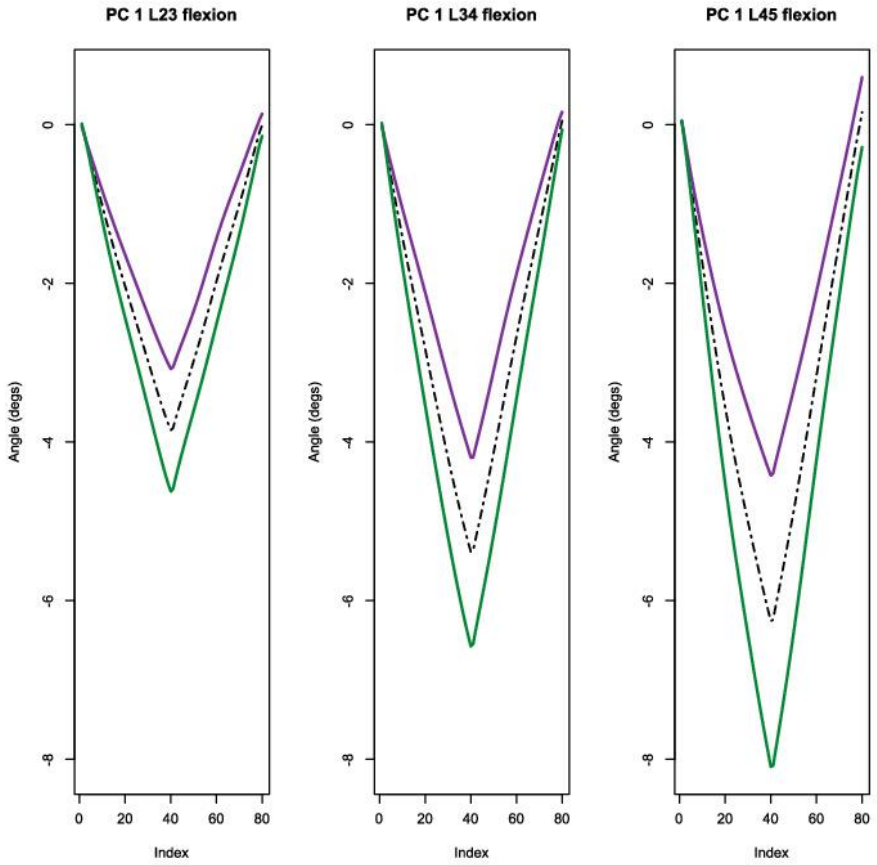

Figure 2: PC 1 flexion. Positive PC scores (green) represent greater than average ROM across all joints. Mean motion: black dotted line, +1 s.d.: green solid line, -1 s.d.: purple solid line. The data index is used as a surrogate for table motion on the horizontal axis.

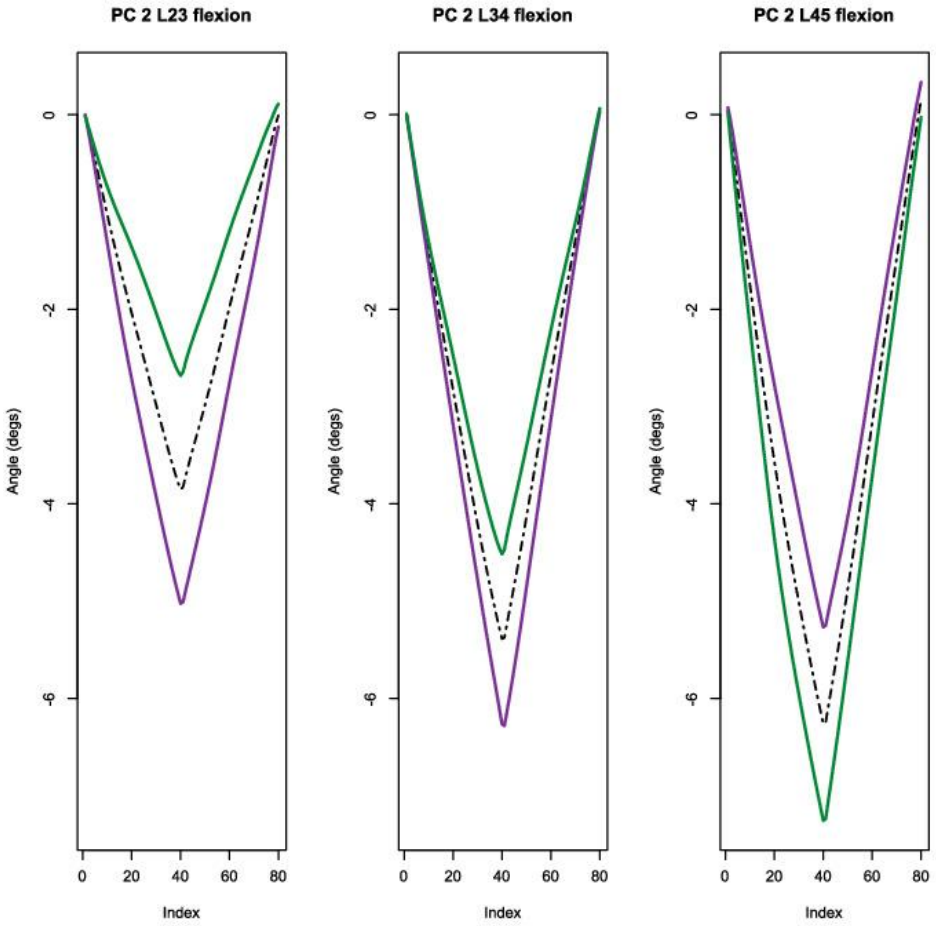

Figure 3: PC 2 for flexion motion. For positive scores (green), ROM is greater than average at L4/5, whilst it is less than average at other joints. Mean: black dotted line, green solid line: +1 s.d., purple solid line: -1 s.d. The data index is used as a surrogate for table motion on the horizontal axis.

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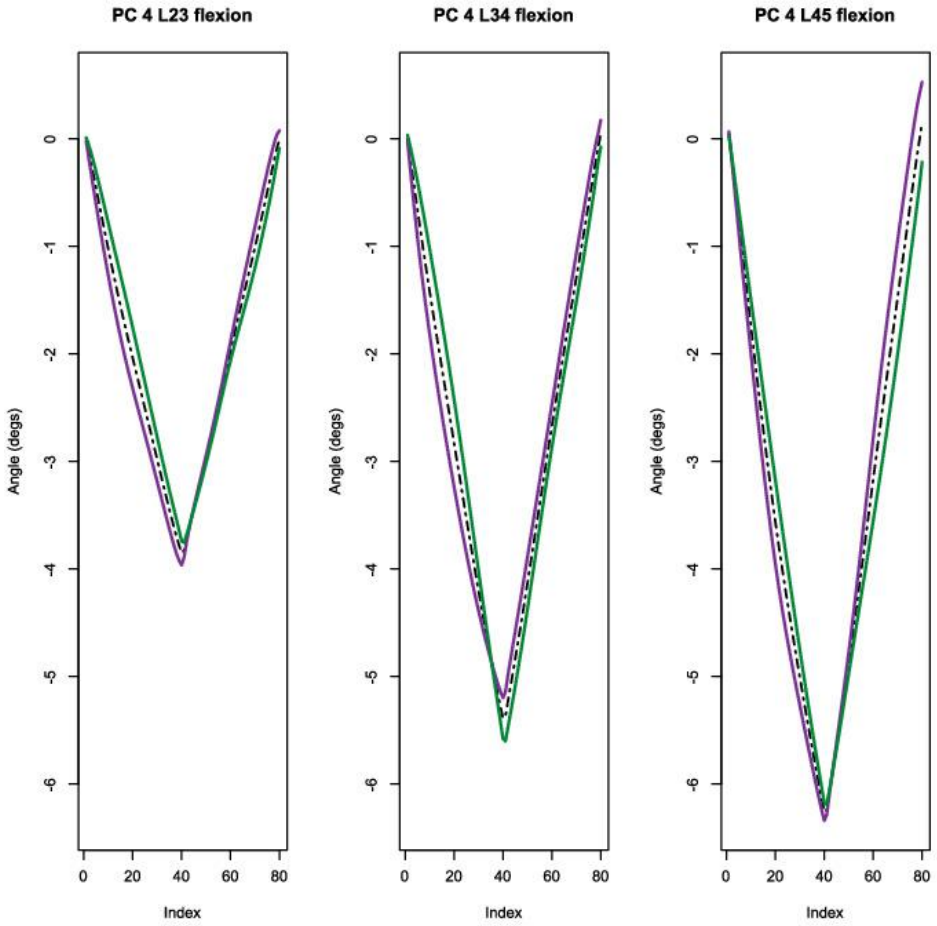

Figure 4: PC 4 for flexion motion. Main feature is variation in the shape of the motion curve, e.g. increased angular velocity (greater negative gradient) of the purple curve during the first part of the motion. Mean: black, green: +1.5 s.d., purple: -1.5 s.d.. The data index is used as a surrogate for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

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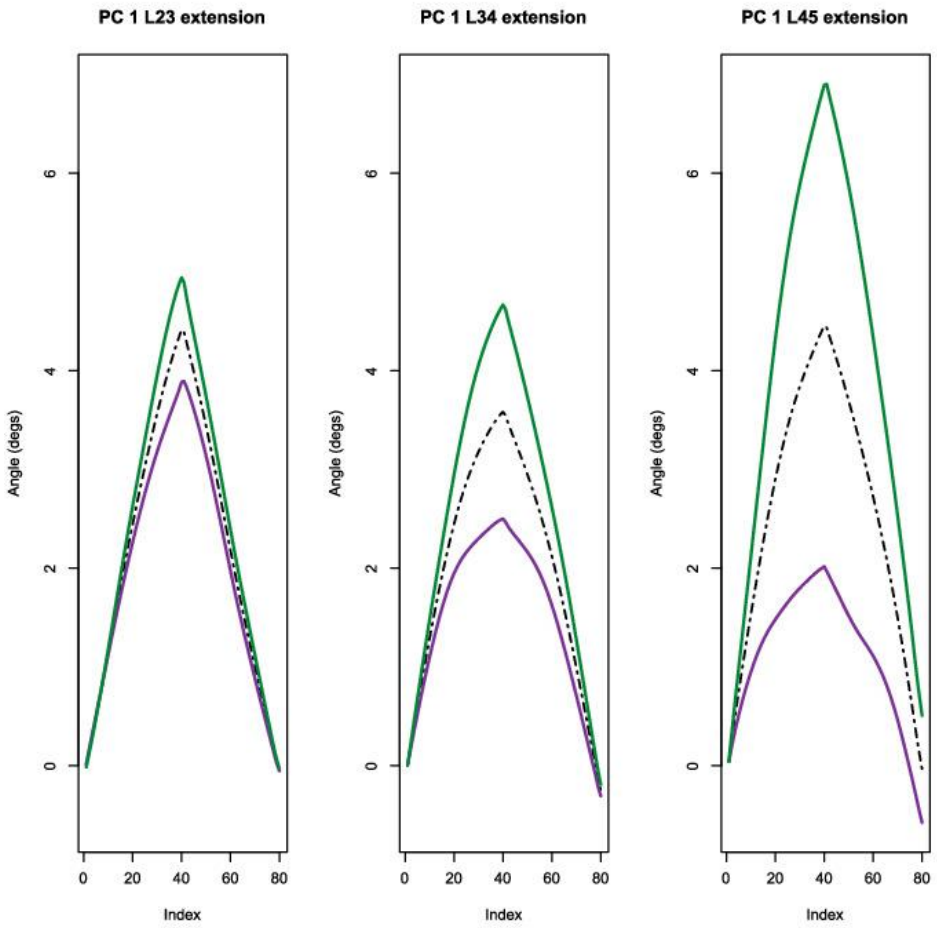

Figure 5: PC 1 extension. Variation in ROM is correlated with some variation in the shape of the motion curve, seen mainly at L4/5, where negative scores are associated with a flattening of the peak & asymmetry. Mean: black, green: +1 s.d., purple: -1 s.d. The data index is used as a surrogate for table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

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186 Representing motion using the first three PC scores, a Hotelling T-squared test was used to compare

187 groups (see table 1). This showed a significant difference between groups for coronal plane motions

188 only ('right' and 'left' motions).

Motion	No. of PCs	T2 statistic	p-value	Perm p-val
extension	3	0.87	0.84	0.84
flexion	3	2.09	0.57	0.58
right	3	10.62	0.02*	0.02*
left	3	9.67	0.03*	0.03*

Table 1: Result of Hotelling T-squared test for group differences. First p-value is based on assumption of multivariate normality, the second is based on a permutation test. The Hotelling T2 test gives nearly identical results to the permutation test. (significant at 0.05 level)*

LDA and QDA Results

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

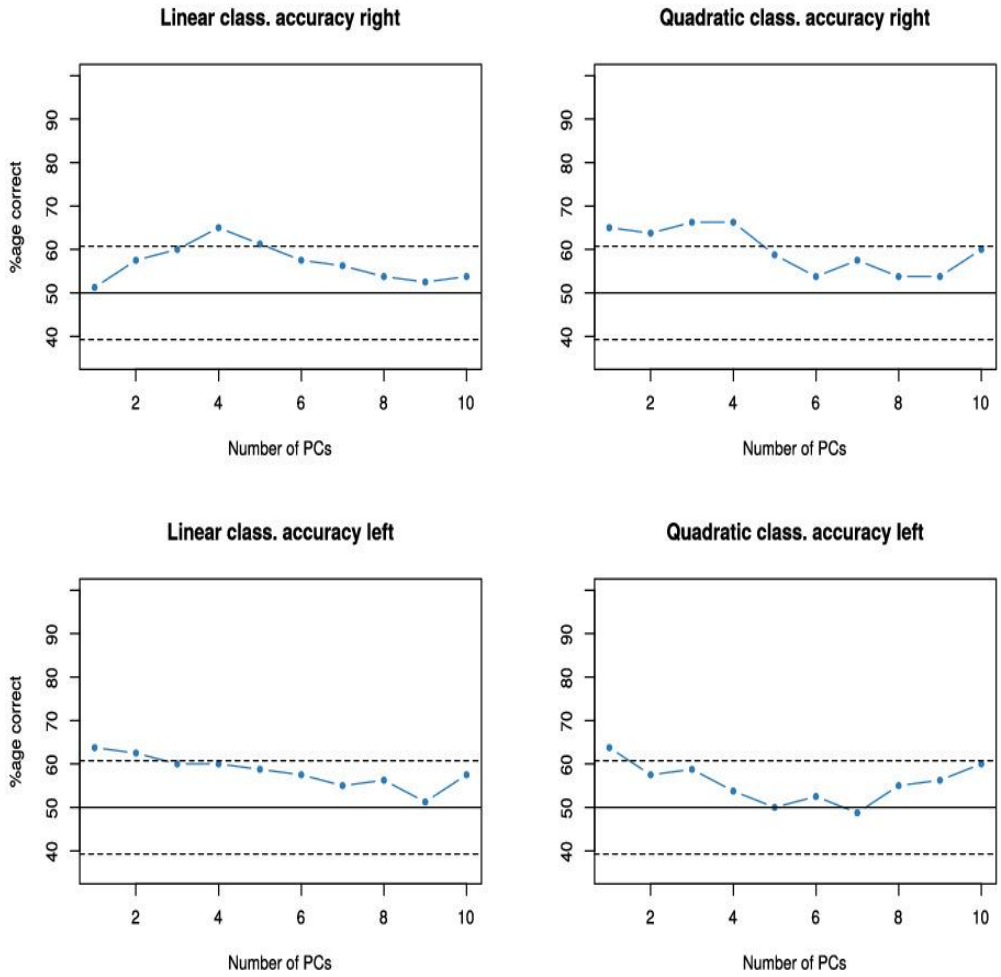

Figure 6: Prediction accuracy (percentage correctly classified) for coronal plane motions using leave-one-out cross-validation versus number of input PCs. Linear (left) and quadratic (right) discriminant analysis. Dotted horizontal lines show the H_0 rejection region; points outside these dotted lines achieve statistical significance at the 0.05 level.

200

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

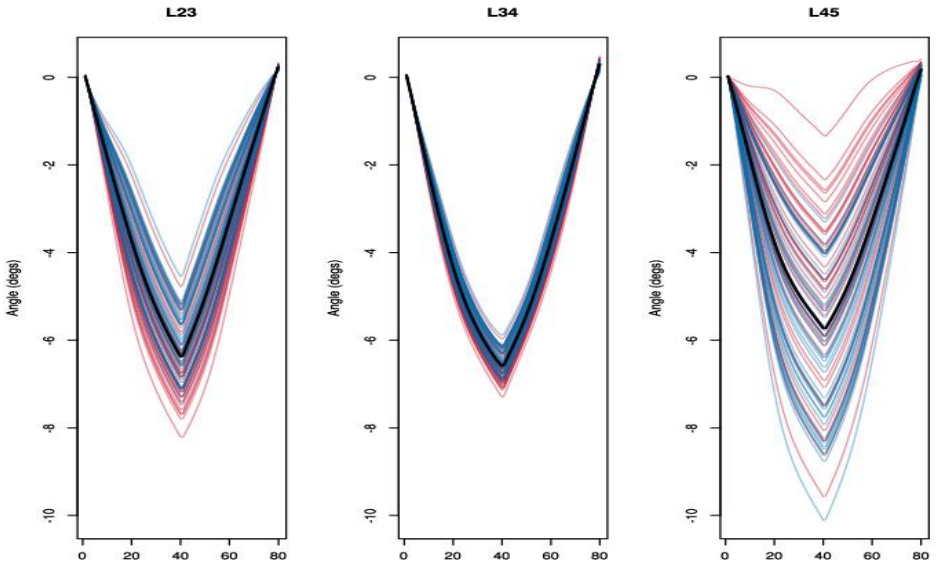

Figure 7: Projection of data onto linear discriminant of the LDA model using the first 2 PCs, 'left' motion. This shows the features by which the two groups differ maximally. The control group (blue) has a smaller ROM at L2/3 and L4/5, but greater ROM at L4/5 than the back pain group (red). The data index is used as a surrogate for table motion on the horizontal axis.

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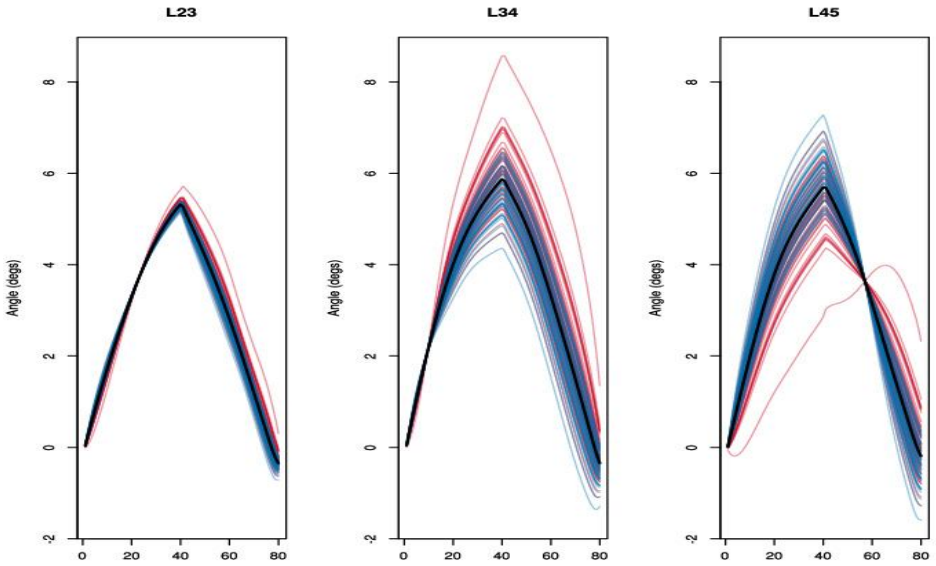

Figure 8: Projection of data onto linear discriminant of LDA model using the first 4 PCs as input, 'right' motion. This shows the features by which the two groups differ maximally. The control group (blue) has a smaller ROM at L3/4, but greater ROM at L4/5. There also appears to be differences in shape 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

The 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 with ROM is unclear, but may indicate that relatively stiff spines have more abnormal motion curves in extension, if one can assume that the shape of the mean motion curve is more normal.

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.

The apparent unimportance of shape differences may be explained by a number of considerations. Firstly, although one might expect an alteration in motion curve shape in those with back pain, due to an expanded neutral zone [24] , 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 [10] .

Secondly, although there was clearly substantial variation in motion curve shapes (see supplementary resources), these differences may be particular to individuals and therefore be distributed arbitrarily across PC dimensions. These shape differences, therefore, may only be understood in the context of subject-specific anatomical and mechanical characteristics. It is the

task of future studies to elicit underlying principles of normal motion, common to all individuals, which takes into account subject-specific variations.

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, 25] . 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 [26] . 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 [27, 28] . 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 [29] . Presumably, the greater force required to obtain the same ROM during imposed passive motions may highlight the influence of passive restraints. In addition, greater reliability for tracking vertebral bodies in coronal plane motions may mean these measurements are less contaminated with noise [7] .

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 differences in passive restraints between vertebrae. Uncovering biomarkers of back pain provides an essential guide to understanding mechanisms in this poorly understood condition. The high dimensionality of QF data requires a variety of analytical approaches to be employed to check previous finding and open new avenues.

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