The association between muscle architecture and muscle spindle abundance

Roger W. P. Kissane[1†*], James P. Charles[1†], Robert W. Banks[2] & Karl T. Bates[1]

[1] Department of Musculoskeletal & Ageing Science, Institute of Life Course & Medical Science, University of Liverpool, The William Henry Duncan Building, 6 West Derby Street, Liverpool L7 8TX, UK

[2] Department of Biosciences and Biophysical Sciences Institute, University of Durham, South Road, Durham DH1 3LE, UK

†Joint first authors

*Correspondence to: r.kissane@liverpool.ac.uk

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19 **Abstract**

20 Across the human body, skeletal muscles have a broad range of biomechanical roles that employ

21 complex proprioceptive control strategies to successfully execute a desired movement. This

22 information is derived from peripherally located sensory apparatus, the muscle spindle and Golgi

23 tendon organs. The abundance of these sensory organs, particularly muscle spindles, is known to

24 differ considerably across individual muscles. Here we present a comprehensive data set of 119

25 muscles across the human body including architectural properties (muscle fibre length, mass,

26 pennation angle and physiological cross-sectional area) and statistically test their relationships with

27 absolute spindle number and relative spindle abundance (the residual value of the linear regression

28 of the log-transformed spindle number and muscle mass). These data highlight a significant positive

29 relationship between muscle spindle number and fibre length, emphasising the importance of fibre

30 length as an input into the central nervous system. However, there appears to be no relationship

31 between muscles architecturally optimised to function as displacement specialists and their provision

32 of muscle spindles. Additionally, while there appears to be regional differences in muscle spindle

33 abundance, independent of muscle mass and fibre length, our data provide no support for the

34 hypothesis that muscle spindle abundance is related to anatomical specialisation.

35

Introduction

Skeletal muscles are comprised of two functionally distinct types of muscle fibre: extrafusal fibres, whose primary role is to generate power and movement; and the intrafusal fibres of muscle spindles, whose principal function is to modify the sensory endings' responses to changes in muscle length [1,2]. Within a single organism, muscles exhibit diverse biomechanical roles, from the large quadriceps and hamstring muscles integral for walking [3] to the smaller muscles of the eye which function to produce rapid eye movements and stabilisation [4]. It is a commonly held belief that the provision of muscle spindles reflects the functional demands of a given muscle [5-8], with some hypothesising that muscles with high spindle densities (number of muscle spindles per gram) are primarily involved in fine motor control [5] or function as kinesiological sensors [6]. There are, however, several fundamental issues with this hypothesis. The first major issue is the use of spindle density to quantify the abundance of spindles within skeletal muscle. Spindle density exhibits a non-linear relationship with muscle mass [9-11] making it highly misleading to infer linear comparisons with muscles of different sizes. Instead, any inference of spindle provision should be based on a suitably transformed linear relationship [12]. Subsequently, the residual value of the linear regression of the log-transformed spindle number and muscle mass as an unbiased measure has become the prevailing descriptor of spindle abundance [10,11,13]. Residual values are homogenously distributed, allow for back-transformation calculations of spindle number, and provide the most unbiased comparative measure of relative spindle abundance [10,11]. The second problem with this hypothesis is the general lack of quantitative data defining muscle function, which is often described in subjective qualitative terms such as 'fine motor control'.

Through the novel application of musculoskeletal modelling of human walking, it has been shown that muscles of the leg considered to be highly abundant in muscle spindles tend to function more like springs, while those less abundant typically functioned more as brakes during overground walking [13]. This provides the first quantitative insight into the potential physiological determinants of muscle spindle abundance. However, muscle spindle abundance not only varies within a single

61   locomotor muscle group but also between muscle groups, where for example muscle spindles are

62   significantly more abundant in axial muscles and those of the neck compared to those of arm, legs,

63   hands and feet [10]. This may be indicative of distinct biomechanical roles or control strategies between

64   anatomical regions [10,11]. Thus, despite the significant correlation of muscle architecture (muscle fibre

65   length and pennation) with muscle spindle number of the leg [13], it cannot be assumed to hold true

66   across the entire human body. Therefore, in this study, we have collated a comprehensive data set of

67   human muscles (119 muscles across nine body regions) describing muscle architecture to test

68   correlations between muscle spindle abundance and muscle anatomy, with the aim of investigating

69   the relationships between muscle architecture, spindle number and spindle abundance.

70   Firstly, given the perception of muscle spindles being primarily length sensors [10,14-17] and the findings

71   in the leg muscle [13] we hypothesise that muscle spindle provision will correlate with anatomical

72   derivatives important to muscle length change across the entire human body (e.g. muscle fibre length

73   and pennation angle), Hypothesis 1. Secondly, using morphospace plots of extrafusal fibre length and

74   PCSA we will determine whether muscles with greater abundances of muscle spindles have

75   architectural properties optimised for function as displacement specialists [18-21] as is often

76   hypothesised, Hypothesis 2 [5-7]. Finally, we test to see if there are differences in functional

77   specialisation across body regions that may account for the heterogeneity in spindle abundance across

78   the body [10], Hypothesis 3.

79

80   **Results**

81   *Architectural correlates of muscle spindle provision (Hypothesis 1-2)*

82   Across all 119 muscles tested, muscle fibre length ($R^2 = 0.27$, P<0.001, Fig. 2a), pennation angle (R^2

83    $= 0.23$, P<0.001, Fig. 2b) and PCSA ($R^2 = 0.16$, P<0.001, Fig. 2c) all presented a significant positive

84   correlation with muscle spindle number. There were, however, no correlations with relative spindle

85 abundance and fibre length (R^2=0.024; P=0.06; Fig. 2a, Supplementary Figure 2a), pennation angle

86 (R^2= 0.001; P=0.36; Fig. 2b, Supplementary Figure 2b) or PCSA (R^2 = 0.005, P=0.16, Fig. 2c,

87 Supplementary Figure 2c). The functional morphospace plots show that across the 119 human

88 muscles there was no clear grouping of muscles based on spindle number (Fig 3a, Supplemental

89 Figure 3) or spindle abundance (Fig 3b, Supplemental Figure 4) with those architecturally optimised

90 to function as displacement specialists (i.e. long muscle fibre length and low PCSA).

91

92 *Heterogeneity in muscle architecture across body regions (Hypothesis 3)*

93 When looking at the distribution of muscle spindle abundance across the newly realised correlate of

94 muscle fibre length and muscle spindle number (Fig. 2a), muscles with a greater relative abundance

95 appear to sit above the regression line, and those with a lower relative abundance appear to sit

96 below this line. We find that muscles in the neck sit above this relationship, while those of the

97 shoulder sit below it (Fig. 4a), consistent with the pattern seen when plotting muscle mass against

98 muscle spindle number [10]. This suggests there exist regional differences in relative spindle

99 abundance when calculated from the relationship between muscle spindle number and fibre length.

100 Therefore, through the generation of fibre length-derived residual values (Fig. 4b) we show that a

101 significant positive relationship exists with those estimated using muscle mass (R^2=0.60, P<0.001,

102 Fig. 4c) and that regional differences exist in muscle spindle abundance when derived from fibre

103 length (Fig. 4d, e). Individual body regions occupied distinct areas across the morphospace plots

104 (Fig. 5a), with significant regional differences in muscle fibre length (F(8) =5.864, P <0.001, Fig.

105 5b) and PCSA (F(8)=8.413, P<0.001, Fig. 5c). There appeared to be no relationship with relative

106 spindle abundance. Finally, anatomical disparity (F(8)=5.402, P<0.001, Fig. 5d) significantly varied

107 across body segments and appeared to show no underpinning relationship with muscle spindle

108 abundance.

109

Discussion

There has been a long-held belief that muscle spindles function primarily as length and velocity sensors and that functional specialisation underpins the number of muscle spindles per unit of mass [17,22]. Recent work has shown that muscle spindle number across the muscles of the leg significantly correlates with muscle fibre length. Additionally, there appears to be a strong association between muscle spindle abundance and the biomechanical function of the muscles during walking [13]. Yet, we still lack an understanding of whether such anatomical correlates hold true across multiple body regions that undergo different locomotor behaviours and central control strategies [10,11,13]. Through the compilation of the most comprehensive architectural dataset of human skeletal muscle, we have uncovered novel correlates with muscle spindle provision. Here we show that across all body regions that absolute muscle spindle number correlates not only with muscle mass but also muscle fibre length, pennation angle and PCSA (Hypothesis 1). Additionally, we find no support for the commonly held belief that muscles optimised to function as displacement specialists have a greater muscle spindle abundance (Hypothesis 2). Finally, we show that muscle spindle abundances derived from fibre length mirror those generated from muscle mass, and subsequently highlight the complexity of muscle architecture and muscle spindle abundance (Hypothesis 3).

126

Anatomical correlates with muscle spindle composition

Here we show that muscle spindle number is significantly related to muscle fibre length, fibre pennation angle and PCSA (Fig. 2). Despite this significant relationship, there does not appear to be any relationship with muscle spindle abundance (Fig. 2, Supplementary Figure 2). It has long been thought that muscle fibre length is a key input signal to the central nervous system [17,22] and the correlations shown here provide statistical evidence of this, thus supporting our first hypothesis.

133   The functional capacity of skeletal muscle is highly influenced by its architectural properties [21],

134   where muscles optimised to generate force are composed of short fibre lengths and large PCSA,

135   compared to muscles specialised to undergo large strain amplitudes that are typically composed of

136   long fibre and small PCSA [18-21,23-25]. It has long been thought that muscles containing a greater

137   number of spindles per unit of mass are specialised to function as displacement specialists or as

138   kinesiological sensors [5,6] without any reliable measure of muscle function having been made. We

139   have recently shown that within the muscles of the human lower limb those exhibiting greater

140   absolute numbers of spindles or their relative abundance are not those architecturally optimised as

141   displacement specialists [13]. Our data here provides evidence that this is consistent across individual

142   muscle groups of the human musculoskeletal system (Supplemental Figure 1 & 2), with muscles

143   containing a greater provision of spindles not necessarily being those optimised to function as

144   displacement specialists, thus rejecting hypothesis 2.

145

146   *Regional differences in muscle spindle abundance*

147   Having identified the significant relationship between muscle spindle number and fibre length, the

148   logical next step was to calculate the residual values of this relationship to see if equivalent regional

149   differences existed to those estimated by Banks [10]. Subsequently, we show that muscle spindle

150   abundance estimated by muscle fibre length-derived residual values (Fig. 4) significantly overlap

151   with those estimated by muscle mass [10], with, for example, muscles in the neck being significantly

152   more abundant in spindles than those of the hand or arm (Fig. 4d,e). By using the residual value,

153   their homogeneous distribution with respect to fibre length (Fig. 4b) and mass [10] provides a

154   systematic and unbiased method to compare the relative abundance of muscle spindle [10,11,13], where

155   previous measures like spindle density are sensitive to increases in muscle size. Given the lack of

156   correlation between muscle fibre length (Fig. 2a), pennation angle (Fig. 2b) and PCSA (Fig. 3b)

157   with relative spindle abundance, it is perhaps not surprising that regional differences in muscle

158   spindle abundance are not predicted by muscle architecture (Fig. 5). These data suggest that no

159   single anatomical correlate with relative spindle abundance exists across the human body,

160   expanding upon previous work limited only to muscles of the leg [13] (Hypothesis 3).

161   There exists an inherent difficulty in uncovering anatomical and functional relationships with muscle

162   spindle provision. This is in part due to the methods of quantification, where data are primarily

163   derived from serial transverse histological sections from human cadaveric preparations which

164   constrains the generation of additional morphometric indices (e.g. muscle fibre length and PCSA).

165   Our novel approach relies on the curation of anatomical data, which we know to be highly variable,

166   especially fibre length which is especially susceptible to error[26]. Additionally, while there is

167   variability across the masses between our two data sets (Supplementary Table 1), the similarities in

168   residual values between those derived from mass and from fibre length are encouraging and would

169   in our opinion unlikely be a result of variability in the data. Despite the development of fluorescently

170   labelled proprioceptive sensory endings in mice [27,28] the relative abundances of muscle spindles

171   within the common laboratory mouse are still unknown for all but a few muscles. Therefore, to further

172   progress our knowledge of physiological determinants of muscle spindle abundance we rely on using

173   the only comprehensive data set spanning 137 human muscles [10]. Through musculoskeletal modelling

174   and simulation of human walking, we recovered novel findings suggesting muscle spindle abundance

175   is underpinned by gross *in vivo* function [13], paving the way for comparable experimentation to be

176   done across body regions (e.g. head/neck [29] *vs.* arm/hand [30]) to explore the biomechanical

177   underpinning of heterogeneity in muscle spindle abundance.

178

Conclusion

179

180   Through the assembly of this comprehensive anatomical data set, we have uncovered novel

181   correlates of muscle architecture and muscle spindle provision. We find no statistical support for the

182 idea that muscles containing larger numbers of muscle spindles are those optimised to function as

183 displacement specialists. Critically, our approach extends on from previous work and has uncovered

184 that there exists a tightly coupled relationship between muscle fibre length and spindle number.

185 These data further emphasise the importance of muscle fibre length as a critical input into the

186 central nervous system, while also highlighting the complexity of physiological determinants of

187 muscle spindle abundance.

188

189 **Methods**

190 *Published Sources*

191 Absolute muscle spindle counts, relative abundance and muscle weights were taken from Banks [10].

192 Absolute muscle spindle counts were originally derived from serial cross-sections of muscle and

193 describes the number of separately identifiable capsular expansions containing sensory innervation

194 [31]. Relative abundance of muscle spindles is calculated as the residual value of the linear regression

195 of the log-transformed spindle number and muscle mass were taken directly from Banks (2006)

196 Appendix 1. Muscle architecture data were compiled from multiple sources [32-49] (see ESM 1). Muscle

197 fibre lengths (L_f) and physiological cross-sectional areas (PCSA) for 119 muscles were collated from

198 human specimens whose muscle mass was near identical to the samples from Banks [10] (R^2=0.95,

199 P<0.001, Fig. 1). Individual muscle masses showed there to be a strong significant relationship across

200 the axial, hand, hip, hyoid/jaw, leg, neck and shoulder (Supplementary Figure 1, Supplementary

201 Table 1), while the arm and foot were not as strongly related. Given that the number of muscle

202 spindles is considered to be fixed at birth [10,50], these subtle differences in the arm and foot muscles

203 are unlikely to impact the conclusions drawn from the work here.

204

Original data

206 Nine subjects were recruited (4 Male, 5 Female; Age: 29 ± 3 years; Body mass: 68 ± 10 kg; Height:

207 175 ± 8 cm; BMI: 21.9 ± 1.8 kgm^{-2}) who provided informed consent prior to participating in the study

208 in accordance with ethical approval from the University of Liverpool's Central University Research

209 Ethics Committee for Physical Interventions (Reference number: 3757). This work was conducted in

210 accordance with the declaration of Helsinki and the regulations set out within the ethical guidelines

211 and that of the journal.

212 Foot muscle architecture data from 5 muscles of the right foot were collected from each subject, as

213 previously described [51]. Briefly, this involved a T1-weighted anatomical turbo spin echo (TSE) MRI

214 sequence to estimate muscle volumes and visualise muscle attachment points. Muscle fibre length for

215 the flexor digitorum brevis, flexor hallucis brevis, abductor hallucis, abductor digiti minimi pedis and

216 adductor hallucis (ESM2) we estimated from muscle belly length using correction factors for muscle

217 fibre length:muscle length [52] and pennation angle [53].

218

Data Analysis

220 Given the role of muscle spindles as length sensors, we expect there to be a strong relationship

221 between muscle spindle provision and measures affecting muscle length change, namely fibre length

222 and pennation angle (Hypothesis 1) akin to that seen in the leg muscles of humans [13]. Model II simple

223 regressions (reduced major axis) were therefore conducted to tests for significant linear relationships

224 between these muscle architecture metrics and spindle composition (absolute spindle number and

225 relative spindle abundance, taken from [10]) and muscle architecture (fibre length and fibre pennation).

226 Using scatter plots of fibre length and PCSA we examine the architectural specialisation of individual

227   muscles [18-21,23-25]. Muscles with long fibre lengths and low PCSA were classed as displacement

228   specialised, long L_f and high PCSA as power specialised and short L_f and high PCSA as force

229   specialised. Here we use the morphospace plots to examine whether muscle spindle provision was

230   associated with muscles whose architecture (fibre length and PCSA) are optimised to function as

231   displacement specialists (i.e. long muscle fibre length and low PCSA, Hypothesis 2). Finally, to

232   discern if regional differences in relative spindle abundance were associated with muscle architecture

233   optimised function, muscles were grouped into categories as described in Banks (2006) (arm, axial,

234   foot, hand, hip, hyoid/jaw, leg, neck and shoulder). The variance in muscle architecture across body

235   segments was described by the disparity of individual muscles in morphospace [54]. Briefly, the

236   disparity of individual limbs is calculated as the mean Euclidean distance of all muscles of a given

237   body segment from the centroid (average x-y position of PCSA *vs.* fibre length). To test for regional

238   differences in muscle architecture (fibre length and PCSA) and morphospace disparity one-way

239   analysis of variation (ANOVA) was employed (Hypothesis 3). Where significance was detected post-

240   hoc comparisons were made using the Bonferroni correction. All linear regressions were completed

241   in R using the 'lmodel2' package, while the ANOVAs were completed using SPSS (v25), with the

242   threshold for statistical significance set to $P < 0.05$.

243   **Author Contribution**

244   R.W.P.K conceptualised the study, collated the data and drafted the manuscript. J.P.C collected and

245   analysed MRI/DTI data, critically reviewed, edited, and approved manuscript. R.W.B critically

246   reviewed, edited, and approved manuscript. K.T.B critically reviewed, edited, and approved
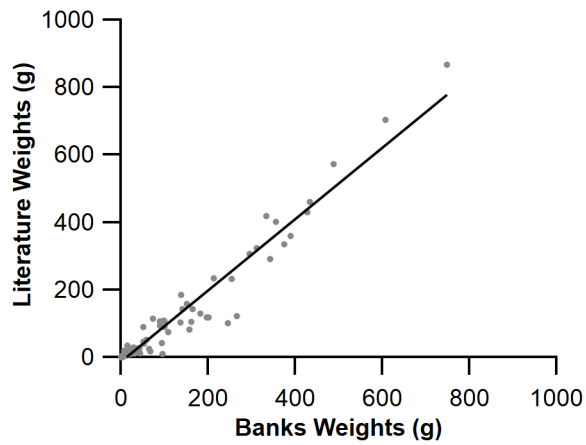
247   manuscript.

248   **Conflict of Interest**

249   All authors confirm that there is no conflict of interest.

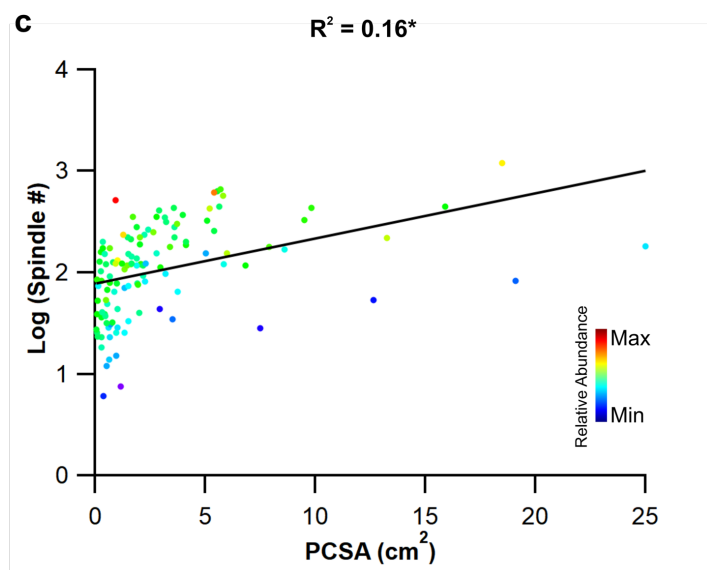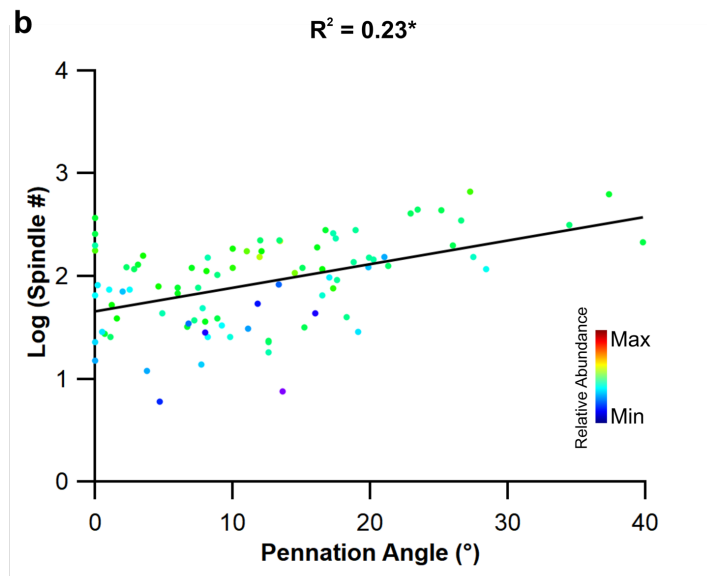250   **Data Availability Statement**
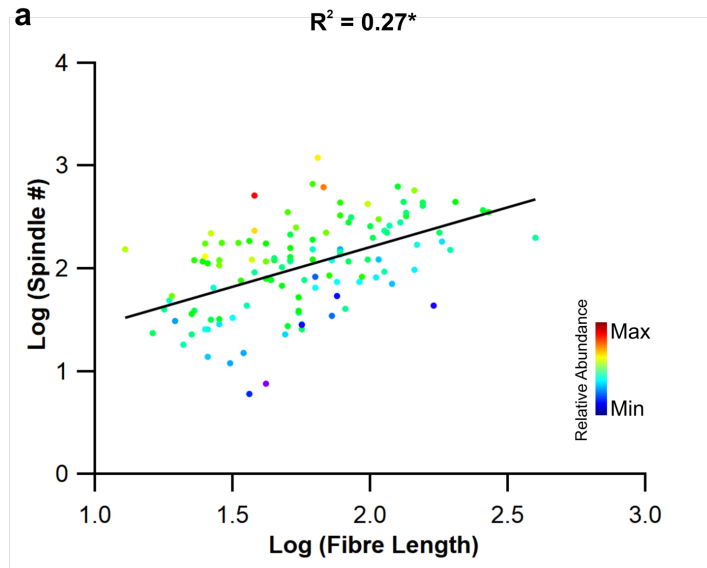
251   All data is contained within the electronic supplementary material (ESM).

252

253

Figure 1. Comparison of muscle masses. Comparison of human muscle masses taken from Banks (2006) and comparative muscle architecture publications (see ESM1). $R^2 = 0.95$, $P < 0.0001$.

a   R² = 0.27*

b   R² = 0.23*

c   R² = 0.16*

256

257 **Figure 2. Muscle spindle number correlates with fibre length, muscle pennation and**

258 **physiological cross-sectional area.** Spindle number is correlated with muscle fibre length (a), muscle

259 pennation (b) and muscle physiological cross-sectional area (c). Muscle spindle abundance as

260 indicated by the heatmap highlights that neither fibre length, muscle pennation nor physiological

261 cross-sectional area correlated with muscle spindle abundance. * P < 0.05.
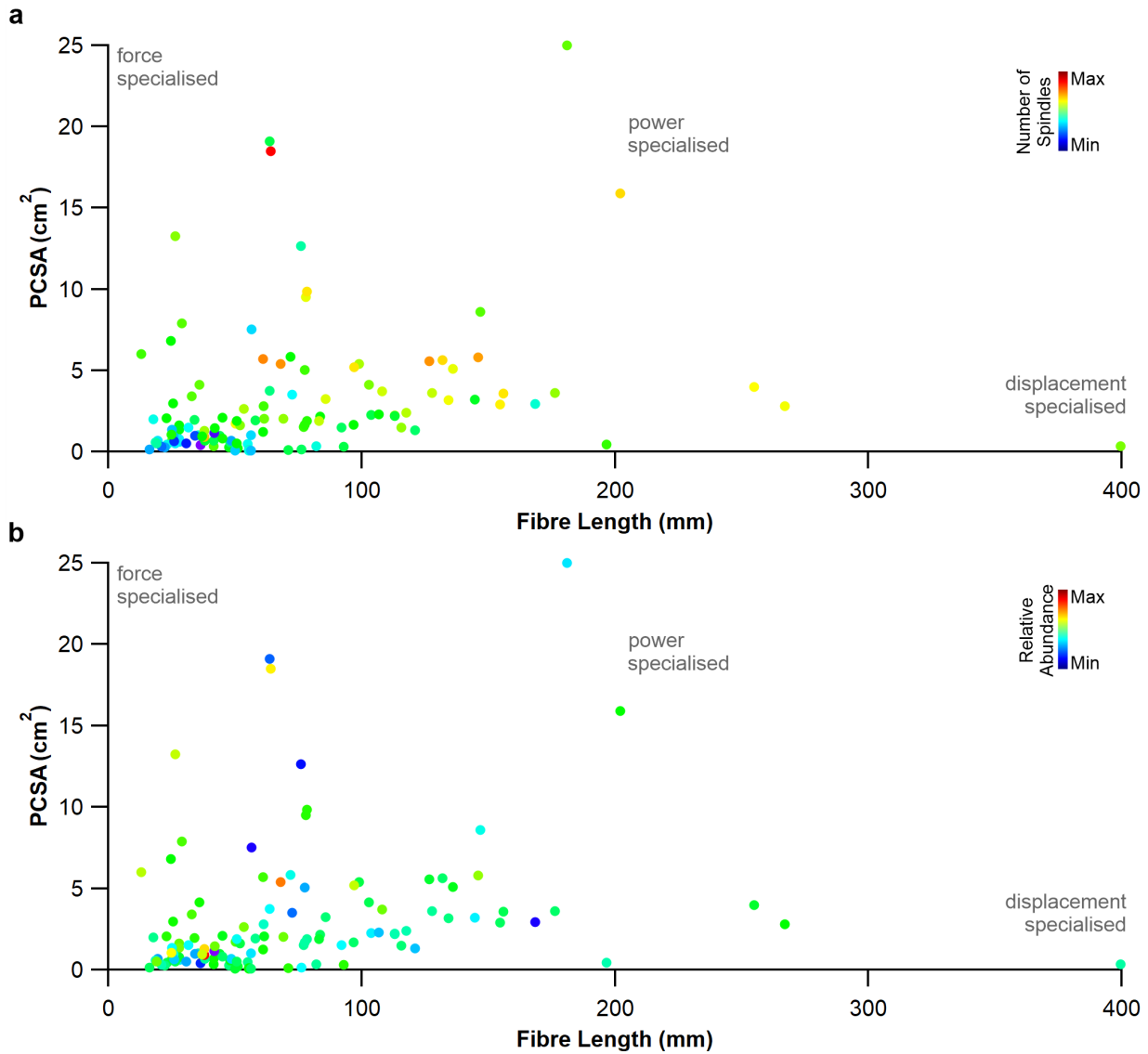
262

263 **Figure 3. Morphospace plots show no correlation between muscle spindle composition with**

264 **displacement specialists.** Muscles that neither contain large absolute numbers of muscle spindles (a)

265 nor are highly abundant in spindles (b) appeared to be preferentially optimised as displacement

266 specialists.

267
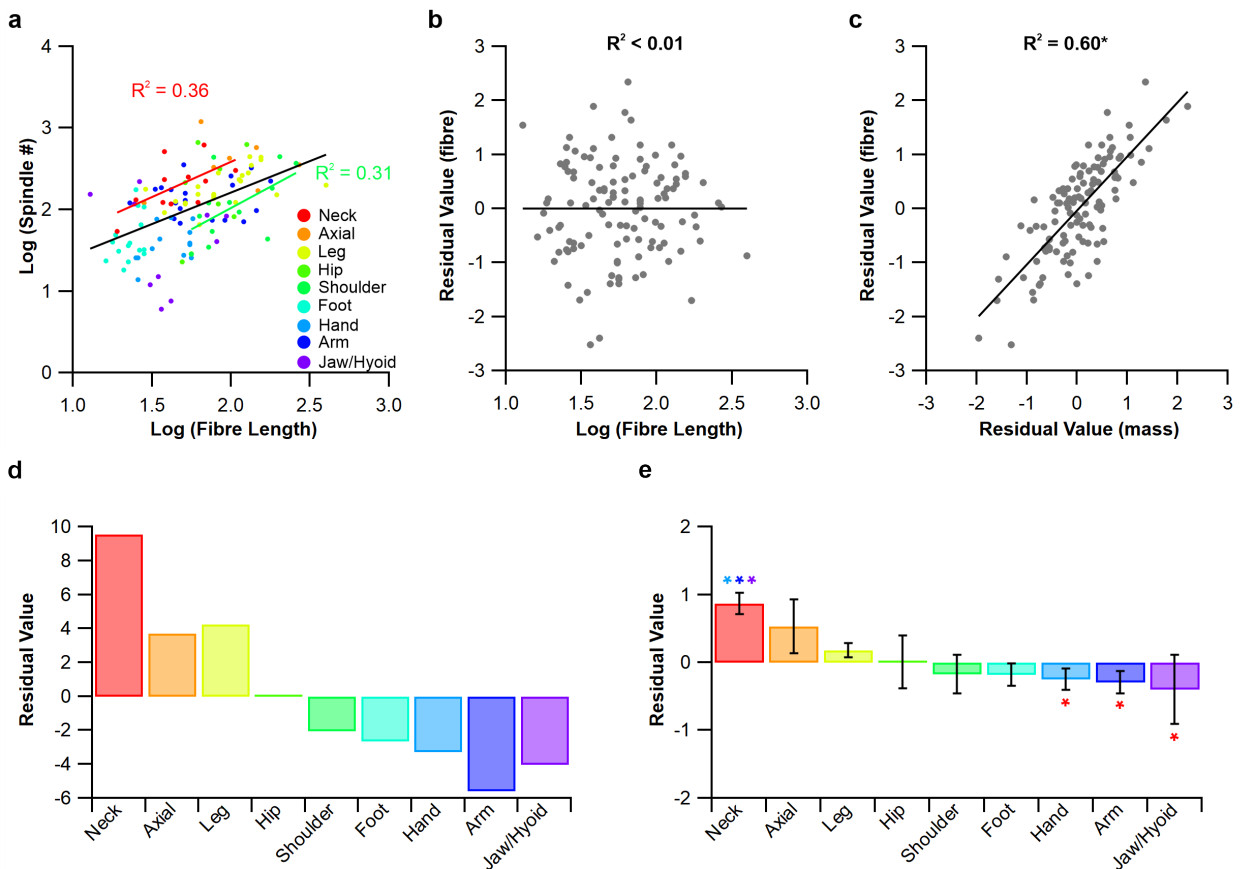
Figure 4. Regional differences in spindle composition. Muscles have been grouped into regions of the body and linear regressions plotted for the neck (red line) and shoulder (green line) (a). These data follow an identical trend to those of Banks (2006) where muscles in the neck appear to be more highly abundant in muscle spindles compared to those of the shoulder. Using the grouped data linear regression (black line) residual values have been calculated for each muscle (b). Taking the residual values estimated by muscle mass from Banks (2006) and those calculated here for fibre length we show that there exists a significant overlap between the two residual value methods (c). This highlights the tightly coupled relationship between muscle spindle number and muscle architecture, while providing further support for the use of residual values as a measure of muscle spindle abundance. The sum (d) and average (e) residual value across regions highlight the difference in abundance across the body. * $P < 0.05$.

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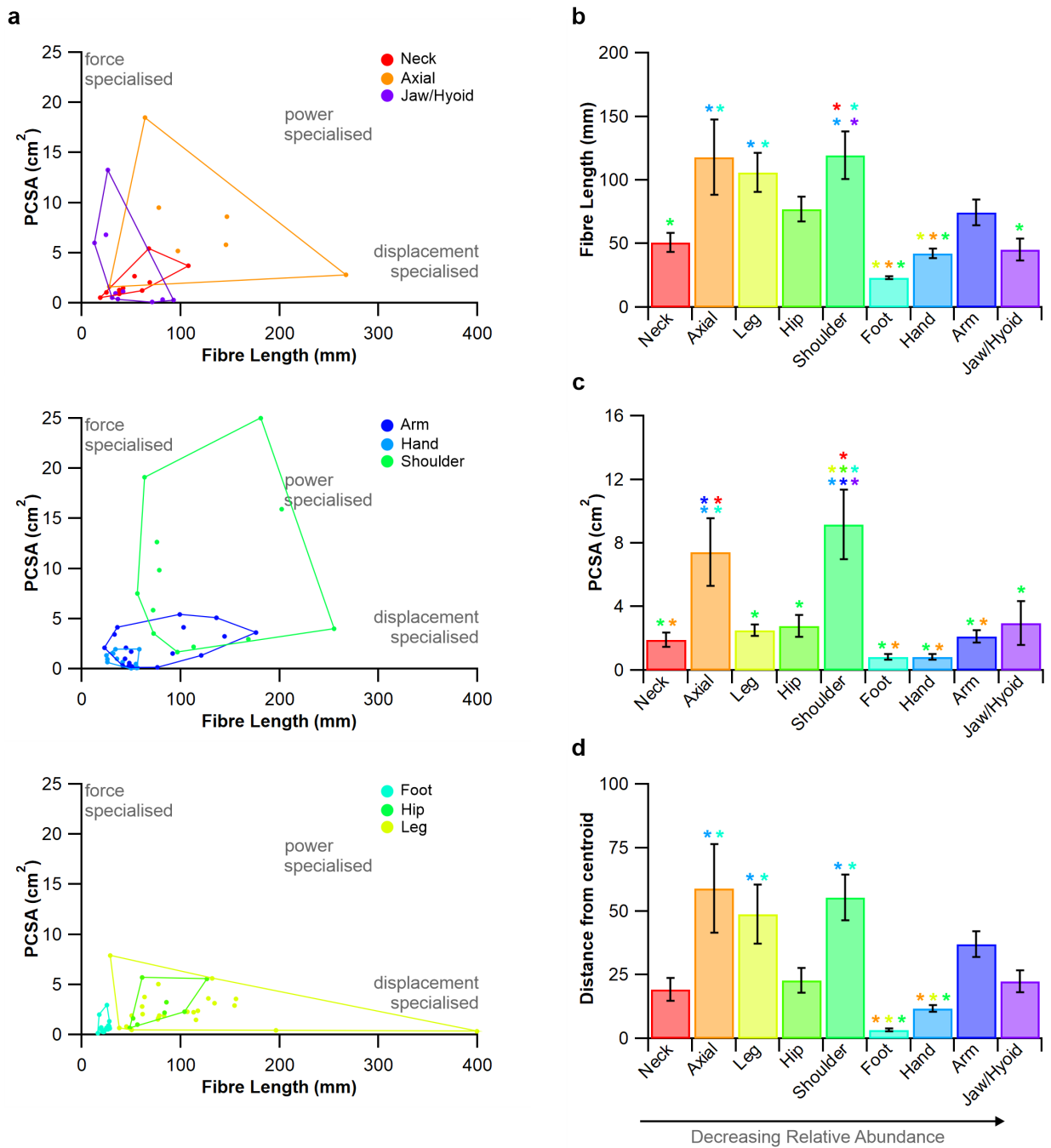
Figure 5. Morphospace plots of regional body parts. To discern potential anatomical parameters that might underpin such regional differences in spindle abundance we have plotted muscle architectural parameters for each of the nine body regions (a). Averaged muscle fibre lengths (b) PCSA (c) and architectural disparity: the mean distance of each individual muscle from the centroid of the outlined area (d). * P<0.05.

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