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Elbow angle modulates corticospinal excitability to the resting biceps brachii at both spinal and supraspinal levels

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27 **New findings**

- 28 • *What is the central question of this study?*

29 Corticospinal excitability to biceps brachii is known to modulate according to upper-limb
30 posture. Here, cervicomedullary stimulation was used to investigate potential spinal
31 contributions to elbow angle dependent changes in corticospinal excitability at rest.

- 32 • *What is the main finding and its importance?*

33 At more extended elbow angles, biceps responses to cervicomedullary stimulation were
34 decreased, whereas cortically-evoked responses (normalised to cervicomedullary-evoked
35 responses) were increased. Results suggest decreased spinal excitability but increased cortical
36 excitability as the elbow is placed in a more extended position, an effect that is unlikely due
37 to cutaneous stretch receptor activation.

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46 **Abstract**

47 Corticospinal excitability to biceps brachii is known to modulate according to upper-
48 limb posture. In Study 1, our aim was to investigate potential spinal contributions to this
49 modulation and the independent effect of elbow angle. Biceps responses to transcranial
50 magnetic stimulation (motor evoked potentials; MEPs) and electrical cervicomedullary
51 stimulation (cervicomedullary motor evoked potentials; CMEPs) were measured at five
52 elbow angles ranging from full extension to 130° of flexion. In Study 2, possible
53 contributions of cutaneous stretch receptors to elbow angle dependent excitability changes
54 were investigated by eliciting MEPs and CMEPs under three conditions of skin stretch about
55 the elbow (stretch to mimic full extension, no stretch, stretch to mimic flexion). Each study
56 had 12 participants. Evoked potentials were acquired at rest with participants seated, the
57 shoulder flexed 90° and forearm supinated. MEPs and CMEPs were normalised to maximal
58 compound muscle action potentials (Mmax). In Study 1, as the elbow was moved to more
59 extended positions, there were no changes in MEPs ($p = 0.963$), progressive decreases in
60 CMEPs ($p < 0.0001$; CMEPs at 130° flexion ~220% of full extension) and increases in
61 MEP/CMEP ratio ($p = 0.019$; MEP/CMEP at 130° flexion ~20% of full extension). In
62 Study 2, there were no changes in MEPs ($p = 0.830$) or CMEPs ($p = 0.209$) between skin
63 stretch conditions. Therefore, while results suggest a decrease in spinal and an increase in
64 supraspinal excitability at more extended angles, the mechanism for these changes in
65 corticospinal excitability to biceps is not cutaneous stretch receptor feedback.

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69 **Abbreviations**

70 CMEP – Cervicomedullary motor evoked potential

71 MEP – Motor evoked potential

72 Mmax – Maximal compound muscle action potential

73 TMS – Transcranial magnetic stimulation

74

75 **Introduction**

76 In humans, corticospinal excitability to upper-limb muscles can be modified by
77 changes in upper-limb posture (Collins & Button, 2018; Collins et al., 2017; Dominici et al.,
78 2005; Forman et al., 2016; Ginanneschi et al., 2005; Ginanneschi et al., 2006; Mazzocchio et
79 al., 2008; Mitsuhashi et al., 2007; Mogk et al., 2014; Nuzzo et al., 2016; Perez & Rothwell,
80 2015; Peterson et al., 2014; Renner et al., 2006). For biceps brachii – a muscle whose length
81 is modified by changes in shoulder, elbow, and forearm position – motor evoked potentials
82 (MEPs) from transcranial magnetic stimulation (TMS) are larger when the forearm is
83 supinated compared to pronated (Mitsuhashi et al., 2007; Mogk et al., 2014; Nuzzo et al.,
84 2016; Peterson et al., 2014), or when the shoulder is in a more flexed or abducted position
85 (Collins & Button, 2018; Collins et al., 2017; Mogk et al., 2014; Nuzzo et al., 2016). Such
86 modifications can be assessed by activating the corticospinal pathway at supraspinal and
87 spinal levels to elicit MEPs and cervicomedullary motor evoked potentials (CMEPs)
88 respectively.

89 Changes in MEPs may reflect changes at any point along the pathway from the cortex
90 to the muscle. Cervicomedullary stimulation on the other hand activates the corticospinal

91 pathway subcortically, and variations in the CMEP reflect changes at a spinal level (Taylor,
92 2006; Ugawa et al., 1991; Ugawa et al., 1994). A recent study showed that CMEPs change in
93 a similar manner to MEPs with different shoulder and forearm orientations (Nuzzo et al.,
94 2016). This suggests that arm posture modulates motoneurone excitability, which likely
95 contributes to changes seen in MEPs. This idea is further supported by a study of
96 anaesthetised monkeys showing modulation of upper-limb muscle responses to cervical
97 spinal cord stimulation as shoulder and elbow position was changed (Yaguchi et al., 2015).
98 Retention of these posture-dependent changes after a high spinal lesion confirmed that they
99 occur without descending influence and suggests that they depend on afferent input (Yaguchi
100 et al., 2015). However, with changes in posture of multiple joints it is difficult to predict
101 which afferents may change and hence, may contribute to altered excitability at a spinal
102 and/or cortical level.

103 Manipulation of the angle of a single joint should simplify the afferent changes
104 associated with altered posture. A few studies have examined the effects of elbow angle on
105 corticospinal excitability to biceps, independent of changes in shoulder and forearm
106 orientation. Of these, cortically-evoked biceps responses were larger in elbow extension than
107 flexion in monkeys (Gellhorn, 1948; Graziano et al., 2004). This change is consistent with an
108 increase in muscle spindle-afferent firing as the muscle stretches with consequent excitation
109 of motoneurons and/or motor cortex (Pierrot-Deseilligny & Burke, 2005). However, the
110 opposite effect has been shown in humans, with larger biceps MEPs reported during elbow
111 flexion in comparison to extension (Renner et al., 2006). Renner et al. suggested the effect
112 may be cortical in origin, given it was not seen in participants with cortical stroke. However,
113 potential spinal contributions cannot be ruled out, particularly as more complex postural
114 changes that shorten biceps and lead to larger MEPs also result in larger CMEPs (Nuzzo et
115 al., 2016). Increased excitability of biceps motoneurons when biceps is shorter suggests that

116 muscle spindles from the homonymous muscle are not the main contributor to posture-related
117 changes in excitability but this has not been confirmed for single-joint changes in posture.
118 Other sensory receptors that fire in relation to joint angle with the muscles at rest include
119 cutaneous and joint receptors, both of which are thought to contribute to perception of limb
120 position. In particular, slowly adapting type II cutaneous receptors respond to skin stretch and
121 can fire monotonically across joint range (Edin, 1992). Hence, these receptors could
122 potentially contribute to joint-angle-related changes in excitability of neurones in the motor
123 pathway. Some evidence for cutaneous afferent influences on motor pathways come from
124 studies showing that physiotherapy taping over the skin can modify muscle activity, although
125 the reported effects are mixed (Constantinou & Brown, 2010; Morris et al., 2013). Further
126 evidence comes from human studies showing the presence of several excitatory and
127 inhibitory cutaneomuscular reflexes, involving indirect cutaneous afferent input to spinal
128 motoneurons (Jenner & Stephens, 1982; Maertens de Noordhout et al., 1992; McNulty et al.,
129 1999). Furthermore, cutaneous afferents have been shown to decrease presynaptic inhibition
130 of Ia afferents (Nakashima et al., 1990) and inhibit propriospinal-like excitatory connections
131 to motoneurons supplying the biceps and other upper limb muscles (Burke et al., 1994;
132 Nielsen & Pierrot-Deseilligny, 1991).

133 Here we aimed to investigate the effects of elbow angle on cortical and spinal level
134 excitability in two studies. In Study 1, we elicited biceps MEPs, CMEPs and Mmax at angles
135 ranging from full extension through to 130° of flexion. We hypothesised that, consistent with
136 effects in more complex postures, CMEPs would be smaller at long biceps muscle lengths
137 produced via single-joint angle changes. In Study 2, a potential contribution of afferent input
138 from cutaneous stretch receptors with different elbow angles was assessed by stretching the
139 skin around the elbow to mimic both flexion and extension, whilst maintaining the elbow at
140 90°.

141 **Materials and methods**

142 **Ethical approval**

143 All individuals presenting to the laboratory gave informed, written consent. Procedures
144 were approved by the Human Research Ethics Committee of the University of New South
145 Wales (HREC number HC14318), and the study was conducted according to the Declaration
146 of Helsinki, except for registration in a database.

147 **Participants**

148 Seventeen healthy individuals presented to the laboratory for Study 1 with five
149 excluded due to the presence of an early latency component of CMEPs, as described in the
150 ‘Cervicomedullary stimulation’ section. Twenty-two healthy individuals presented to the
151 laboratory for Study 2, with ten excluded due to discomfort from stimulation or the presence
152 of an early latency component of CMEPs. Twelve participants completed each study (Study 1:
153 aged 25 y (SD 4), 5 F; Study 2: aged 27 y (SD 5), 8 F) with one completing both studies. All
154 were right hand dominant in Study 1. Ten were right-hand dominant and two were left-hand
155 dominant in Study 2.

156 **Experimental setup**

157 Participants sat upright with the right shoulder flexed at 90° and the forearm supinated.
158 The arm was secured with straps at both the wrist and palm to an arm bar that allowed
159 movement of the elbow joint (Fig 1A). The arm bar allowed the arm to be fixed at angles
160 ranging from 0° of flexion (arm straight) to 130° of flexion, in increments of 5°. Participants
161 were asked to keep their arm relaxed for the duration of each study. Electromyographic activity
162 was recorded from the right biceps brachii through 20-mm diameter Ag-AgCl surface
163 electrodes (Conmed, NY, USA) which were placed over the muscle belly (motor point) and
164 distal tendon. Electrodes were attached with the arm in full extension, and a marker was used

165 on the skin surrounding each electrode so that any electrode displacement could be detected
166 and corrected. Once electrodes were attached, the arm was fixed at 90° of elbow flexion for the
167 remainder of the setup. EMG signals were amplified (x 300), filtered at 16-1000 Hz (CED 1902
168 amplifier; Cambridge Electronic Design, Cambridge, UK), sampled at 5 kHz, and recorded on
169 a computer for analysis (CED 1401 with Signal software; Cambridge Electronic Design).

170 For Study 2, the posture of the upper-limb and the placement of the biceps recording
171 electrodes were identical to that in Study 1. However, the elbow was fixed at 90° of elbow
172 flexion throughout Study 2. Similar to methods used in previous studies (Collins & Prochazka,
173 1996; Collins et al., 2005), skin stretch was applied via pieces of Leuko sports tape (2.5 cm
174 width; Beiersdorf, North Ryde, Australia) attached to the skin at various locations near the
175 elbow (Fig 1A). The pieces of tape were punctured by papers clips which were then attached
176 to strings. The skin could then be stretched by pulling on the strings and tying them to hooks
177 on the apparatus.

178 **Brachial plexus stimulation**

179 A constant current stimulator (Model DS7AH, Digitimer, Welwyn Garden City, UK)
180 delivered single stimuli (200- μ s pulse width) to peripheral nerves supplying right elbow flexors
181 through Ag-AgCl surface electrodes (20-mm diameter, Conmed), placed in the supraclavicular
182 fossa over the brachial plexus (cathode) and over the acromion (anode). Stimulus intensity was
183 increased until no further increase was seen in the compound muscle action potential recorded
184 from biceps, and 120% of this intensity was used to elicit maximal compound muscle action
185 potentials (Mmax). Intensities of 108 mA (SD 20) were used for Study 1 and 68 mA (SD 31)
186 for Study 2. Brachial plexus stimulation setup was done with the elbow fixed at 90°. However,
187 to ensure Mmax was achieved at all angles in Study 1, the intensity for Mmax was also tested
188 in the most extended and flexed positions and was adjusted if necessary.

189 **Transcranial magnetic stimulation (TMS)**

190 To activate the corticospinal pathway at the level of the primary motor cortex,
191 transcranial magnetic stimulation (TMS) was used. A large, bent figure-eight coil (12-cm
192 outside loop diameter; Magstim 200, Magstim, Whitland, UK) was positioned over the left
193 motor cortex at the optimal site to elicit right biceps responses (i.e. the position that produced
194 the largest, most consistent responses). The coil was placed 45° from midline, handle
195 backwards, to induce a posterior-to-anterior current in the brain. TMS intensity (Study 1: 75%
196 (SD 13) of maximum stimulator output; Study 2: 65% (SD 11)) was set to elicit biceps motor
197 evoked potentials (MEPs) of ~ 0.5 to 1 mV (~ 5% of Mmax) when in the 90° position.

198 **Cervicomedullary stimulation**

199 To activate the corticospinal pathway at a spinal level, cervicomedullary stimulation
200 was used. Ag-AgCl surface electrodes (20-mm diameter, Conmed) were placed behind each
201 ear, 1-2 cm posterosuperior to the tips of the mastoid processes (Ugawa et al., 1991). Onset
202 latency was monitored throughout to ensure responses were the result of corticospinal axon
203 stimulation; as an earlier latency (by ~2 ms) indicates motoneurone stimulation at cervical roots
204 (Taylor & Gandevia, 2004). Intensity (Study 1: 160 mA (SD 32); Study 2: 136 mA (SD 40))
205 was set to elicit biceps cervicomedullary motor evoked potentials (CMEPs) of ~ 1 to 2 mV
206 (~ 10% of Mmax) when in the 90° position. In Study 1, we also acquired CMEPs (stimulus
207 intensity: 140 mA (SD 24)) that were matched in size to the MEP (termed “matched CMEPs”
208 throughout this paper).

209 **Study design**

210 Studies 1 and 2 were both single session studies that incorporated repeated measures, crossover
211 designs. During each session, the effects of five different elbow angles (Study 1) or three
212 different skin stretch conditions (Study 2) were examined in random order in each individual.

213 **Protocol**

214 *Study 1*

215 Each participant's full range of elbow flexion (12° (SD 10) to 150° (SD 8)) was measured with
216 a goniometer, and five angles were selected for the study accordingly. The angle on the arm
217 bar (in the flexion direction) closest to a participant's full extension (15° (SD 10)) was used as
218 the reference. All participants were tested at 90° , as this is a common angle used in human
219 studies of elbow flexors and all were tested at 130° despite being able to flex further, given this
220 was the limit of the arm bar. Two other angles were tested, halfway between full extension and
221 90° (50° (SD 5)) and between 90° and 130° (110° for all participants). Each angle was tested
222 twice per session, in random order within two blocks, so that the arm bar changed position ten
223 times. Between each position change, the arm bar was moved up and down several times to
224 avoid any thixotropic effects from the previous angle. At each position, a set of stimuli (5
225 CMEPs, 1 Mmax and 10 MEPs at 0.1 Hz) was delivered so that two sets of responses were
226 elicited per angle (Fig 1B). For the full extension, 90° and 130° angles, an additional 5 CMEPs
227 matched to the size of MEPs were also elicited per set (0.1 Hz). Thus, the total number of
228 evoked responses for each condition was 10 CMEPs, 2 Mmax and 20 MEPs, with an additional
229 10 matched CMEPs for full extension, 90° and 130° angles.

230 *Study 2*

231 To examine whether afferent feedback from cutaneous stretch receptors affected
232 evoked responses of the motor pathway, three skin stretch conditions were utilized. The upper-
233 limb posture for all three conditions was identical. One condition involved no skin stretch. The
234 other two conditions involved stretching the skin about the elbow to mimic the amount of skin
235 stretch that occurs naturally when the elbow is fully extended or fully flexed. This amount was
236 quantified during pilot testing in two individuals by placing marks on skin of the anterior and

237 posterior arm and forearm and then measuring how far each mark moved relative to a mark
238 placed on the elbow, when the elbow was fully extended or flexed compared to 90°.

239 For the condition that involved stretching the skin to mimic elbow extension, the skin
240 of the anterior arm was pulled proximally 2.8 cm (SD 0.6) (pilot testing showed anterior arm
241 skin stretch of 2.1 cm (0.4) with full elbow extension), and the skin of the anterior forearm was
242 pulled distally 3.3 cm (SD 0.7) (pilot testing showed anterior forearm skin stretch of 3.6 cm
243 (0.4)). This stretched the skin across the anterior of the elbow. During this condition, the skin
244 of the posterior arm was pulled distally, and skin of the posterior forearm was pulled proximally
245 to compress the skin across the posterior of the joint. However, accurate measurements of
246 compression amounts were not obtained due to the design of the arm bar. For the condition
247 that involved stretching the skin about the elbow to mimic elbow flexion, the skin of the
248 posterior arm was pulled proximally 2.9 cm (SD 0.6) (pilot testing showed posterior arm skin
249 stretch of 0.8 cm (0.3) during full elbow flexion), and the skin of the posterior forearm was
250 pulled distally 2.6 cm (SD 0.6) (pilot testing showed posterior forearm skin stretch of 0.3 cm
251 (0.5)).

252 The order of the three skin-stretch conditions was randomized. In each condition, two
253 sets of evoked responses were collected (Fig 1C). Each set consisted of 5 CMEPs, 10 MEPs,
254 and 2 Mmax. Thus, the total number of evoked responses for each condition was 10 CMEPs,
255 20 MEPs, and 4 Mmax.

256 **Data analysis and statistics**

257 Individual MEP and CMEP traces were excluded if the root mean square amplitude of
258 EMG for 100 ms before stimulation was ≥ 0.004 mV, after a digital, second-order Butterworth
259 notch filter (bandstop 49 – 51 Hz) was applied to remove any 50-Hz noise (as per Nuzzo et al.,
260 2016). This criterion ensured that the final data set included only those trials in which the

261 muscle was relaxed prior to the elicited potential. All of a participant's MEP or CMEP data
262 were excluded from analyses if they had > 10 MEPs or > 5 CMEPs excluded within at least
263 one angle or stretch condition (Study 1: one participant's MEP and CMEP data excluded; Study
264 2: one participant's MEP data excluded, one participant's CMEP data excluded, and one
265 participant's MEP and CMEP data excluded). From the remaining participants a total of 6 of
266 1100 MEPs and 13 of 880 CMEPs were excluded from Study 1 and a total of 24 of 600 MEPs
267 and 37 of 300 CMEPs were excluded from Study 2. Mean MEP and CMEP areas were
268 calculated for each set. Peripheral changes in muscle fibre action potentials or in the position
269 of surface electrodes with respect to the underlying muscle were accounted for by normalising
270 MEP and CMEP areas to the area of Mmax delivered within the same set. Mean Mmax, MEP
271 (% Mmax) and CMEP (% Mmax) areas were calculated for each angle or stretch condition. In
272 Study 1, matched CMEPs were treated in the same way as for larger CMEPs. The MEP/CMEP
273 ratio was calculated using MEP and matched CMEP areas.

274 Normality was assessed via visual inspection of histograms and the Shapiro-Wilks test.
275 Where the assumption of normality was met, one-way repeated-measures ANOVAs were used
276 to compare the effect of angle or stretch condition on the various outcome measures, with a
277 Greenhouse-Geisser correction applied if the assumption of sphericity was not met. When the
278 assumption of normality was not met, non-parametric Friedman's ANOVAs were used. In
279 Study 1 the angle conditions were as follows: full extension, mid extension, 90°, 110° and 130°
280 (for Mmax, MEP (% Mmax) and CMEP (% Mmax) areas) or full extension, 90° and 130° (for
281 matched CMEP area (% Mmax) and MEP/CMEP ratio). In Study 2 the stretch conditions were
282 as follows: 90° with skin stretch to mimic full extension, 90° with no skin stretch and 90° with
283 skin stretch to mimic flexion (for Mmax, MEP (% Mmax) and CMEP (% Mmax) areas). For
284 post-hoc analyses, Bonferroni corrected two-tailed, paired-samples t-tests (normal data) or
285 two-tailed Wilcoxon signed-rank tests (non-normal data) were used to compare the reference

286 condition (full extension or 90° with skin stretch to mimic full extension) to each other
287 condition. Statistical analyses were performed using IBM SPSS Statistics software (version
288 23). Group data are expressed as mean (SD) and statistical significance was set at $p < 0.05$.

289

290 **Results**

291 **Study 1**

292 Areas and peak-to-peak amplitudes of Mmax, MEPs, CMEPs, and matched CMEPs
293 for each angle condition are given in Table 1. Mmax area was different between angles
294 ($F_{(1.27,14.00)} = 14.83, p = 0.001, n = 12$, Fig 2 and 3A), with larger Mmax at full extension in
295 comparison to mid extension ($p = 0.028$; ~92% of full extension), 90° ($p = 0.019$; ~77% of
296 full extension), 110° ($p = 0.005$; ~67% of full extension) and 130° ($p = 0.007$; ~66% of full
297 extension). Similar differences between angles were seen for Mmax amplitude ($F_{(1.65,18.12)} =$
298 $11.52, p = 0.001, n = 12$), with larger Mmax at full extension in comparison to 90°
299 ($p = 0.023$), 110° ($p = 0.004$) and 130° ($p = 0.008$). But unlike area, amplitude at full
300 extension was not different in comparison to mid extension ($p = 0.060$).

301 MEP area and amplitude (% Mmax) were not different between angles (area: $\chi^2(4) =$
302 $0.66, p = 0.963, n = 11$, Fig 2 and 3B; amplitude: $\chi^2(4) = 3.13, p = 0.560, n = 11$).

303 CMEP area (% Mmax) was different between angles ($\chi^2(4) = 33.67, p < 0.0001,$
304 $n = 11$, Fig 2 and 3B), with smaller CMEPs at full extension in comparison to 90° ($p = 0.004$;
305 ~156% of full extension), 110° ($p = 0.004$; ~183% of full extension) and 130° ($p = 0.008$;
306 ~219% of full extension), but not mid extension ($p = 0.824$; ~109% of full extension). Similar
307 differences were seen for CMEP amplitude ($\chi^2(4) = 36.44, p < 0.0001, n = 11$), with smaller
308 CMEPs at full extension in comparison to 90° ($p = 0.004$), 110° ($p = 0.004$) and 130° ($p =$
309 0.004), but not mid extension ($p = 0.699$).

310 Matched CMEP areas were different between angles ($\chi^2(2) = 16.55, p < 0.0001, n =$
311 11), with smaller CMEPs at full extension in comparison to 90° ($p = 0.002$; ~189% of full
312 extension) and 130° ($p = 0.004$; ~376% of full extension). Similar differences were seen for
313 matched CMEP amplitude ($\chi^2(2) = 20.18, p < 0.0001, n = 11$), with smaller CMEPs at full
314 extension in comparison to 90° ($p = 0.002$) and 130° ($p = 0.002$).

315 As was planned, there were no differences ($p = 0.765$) between matched CMEP and
316 MEP areas elicited in the 90° position (Wilcoxon signed-rank test), indicating they were
317 similar in size. The MEP/CMEP ratios were different between angles ($F_{(1.05,10.47)} = 7.48,$
318 $p = 0.019, n = 11$), with larger values at full extension in comparison to 90° ($p = 0.048$; ~29%
319 of full extension) and 130° ($p = 0.036$; ~19% of full extension).

320 **Study 2**

321 Areas and peak-to-peak amplitudes of Mmax, MEPs and CMEPs for each stretch
322 condition are given in Table 1. Mmax area and amplitude were not different between skin
323 stretch conditions (area: $F_{(1.25,13.72)} = 1.12, p = 0.325, n = 12$, Fig 4A; amplitude: $F_{(1.19,13.10)} =$
324 3.08, $p = 0.098$). MEP area and amplitude were not different between skin stretch conditions
325 (area: $F_{(1.25,11.21)} = 0.19, p = 0.727, n = 10$, Fig 4B; amplitude: $F_{(2,18)} = 0.02, p = 0.977$).
326 CMEP area and amplitude were not different between skin stretch conditions (area: $F_{(2,18)} =$
327 1.71, $p = 0.209, n = 10$, Fig 4B; amplitude: $F_{(2,18)} = 1.64, p = 0.221$).

328

329 **Discussion**

330 Results presented here show that elbow angle modulates the excitability of motor
331 pathways supplying the relaxed biceps brachii. At more extended elbow angles, Mmax was
332 increased, MEPs were unchanged, both large and small CMEPs were decreased, and the
333 MEP/CMEP ratio was increased in comparison to more flexed angles. The opposite effects of

334 elbow angle on CMEPs and the MEP/CMEP ratio suggest decreased spinal-level excitability
335 with elbow extension, but an increase in supraspinal excitability. Changes are unlikely due to
336 afferent input from cutaneous stretch receptors, as shown by a lack of change in MEPs and
337 CMEPs under different skin stretch conditions in Study 2.

338 In Study 1, Mmax was largest in full extension, becoming progressively smaller as the
339 elbow was flexed. Changes in Mmax occur as a muscle lengthens or shortens (Frigon et al.,
340 2007). Biceps Mmax is larger when the shoulder is flexed in comparison to no flexion
341 (Collins & Button, 2018; Collins et al., 2017; Nuzzo et al., 2016) but there are mixed reports
342 for forearm orientation, with Mmax in supination reported as both larger (Mogk et al., 2014)
343 and smaller (Nuzzo et al., 2016) than pronation. Overall, these studies report larger Mmax for
344 shorter biceps lengths. This contrasts with results from the current study, given we observed
345 smaller Mmax at shorter biceps lengths. It is likely that the specific electrode positions used
346 in the different studies account for the differing findings as the changes in Mmax reflect the
347 combined effects of changes in muscle length on the shape of the muscle fibre action
348 potentials and changes in the location of the underlying muscle with respect to the surface
349 electrodes. Here, during setup, biceps recording electrodes were placed on the skin when the
350 arm was in full extension. Thus, the location of electrodes would have been optimal in this
351 position and may have become less optimal as the elbow was moved to more flexed
352 positions, resulting in progressively smaller responses. This highlights the importance of
353 normalising MEPs and CMEPs to Mmax.

354 Opposite to Mmax, biceps CMEPs were smallest in full extension and became
355 progressively larger as the elbow was flexed (i.e. biceps shortened). This is consistent with
356 previous work, which showed larger CMEPs when the shoulder was more flexed or when the
357 forearm was more supinated (i.e. biceps shortened) in a study where posture at both joints
358 was altered (Nuzzo et al., 2016). By contrast, no changes in CMEPs (% Mmax) were seen

359 when the shoulder was flexed while the elbow angle was maintained (i.e. biceps shortened)
360 (Collins et al., 2017). Thus, it is possible that elbow angle contributes more than shoulder
361 orientation to modifications in the excitability of biceps motoneurons. Moreover, biceps
362 muscle length may not be a critical factor that leads to altered biceps motoneurone
363 excitability with change of posture.

364 Unlike CMEPs, MEP size was not influenced by changes in elbow angle. MEPs and
365 CMEPs are shown to activate many of the same corticospinal axons supplying biceps
366 motoneurons, and spinal contributions to the MEP may be partially accounted for by
367 normalising MEPs to CMEPs (MEP/CMEP ratio) (Gandevia et al., 1999; Taylor et al., 2002).
368 Here, when the MEP and CMEP were matched in size to allow this comparison, the
369 MEP/CMEP ratio was largest at full extension and became progressively smaller as the
370 elbow was flexed. This suggests that supraspinal mechanisms probably contributed to
371 changes in corticospinal excitability in an opposing manner to changes at the spinal level.
372 The lack of effect of elbow angle on MEP size seen here is in contrast to previous studies in
373 humans, which report larger MEPs at shorter biceps lengths (shoulder flexed, elbow flexed or
374 forearm supinated) (Collins et al., 2017; Mogk et al., 2014; Nuzzo et al., 2016; Renner et al.,
375 2006). However, an increase in supraspinal excitability with biceps lengthening is in line with
376 studies in the rat (Sanes et al., 1992) and monkey (Gellhorn, 1948; Graziano et al., 2004).
377 Moreover, although Nuzzo et al. (Nuzzo et al., 2016) reported smaller MEPs at longer biceps
378 lengths, MEP/CMEP ratios were larger at longer biceps lengths, as in the current study,
379 although differences were not statistically significant.

380 The precise mechanisms of posture-related changes in CMEPs and MEPs remain
381 unknown. The simplest explanation for differences in CMEPs with the arm held passively at
382 different elbow angles is that altered afferent input changes excitability of motoneurons or
383 premotoneurons in the corticospinal-motoneuronal pathway. Thus, afferent inputs from

384 joint, skin and muscle receptors, and various pathways of neuronal integration at spinal and
385 supraspinal levels are all potential contributors. Perception of passive joint angle is thought to
386 rely on the combined firing of muscle spindle receptors (primary and secondary endings) in
387 muscles on both sides of the joint, slowly adapting type II (SAII) cutaneous receptors which
388 signal skin stretch and stretch receptors in the joint capsule and ligaments (Proske &
389 Gandevia, 2012). Muscle spindle (group Ia and II) and SAI afferent firing is monotonically
390 related to joint angle (Burgess et al., 1982; Edin, 1992), whereas joint receptors are active at
391 the extremes of joint range (Burke et al., 1988) and may be unable to provide joint position
392 information within physiological ranges (Proske & Gandevia, 2012).

393 Changes in muscle spindle firing cannot explain the changes in CMEPs across elbow
394 angles. An increase in stretch-induced muscle spindle input from biceps should facilitate biceps
395 motoneurons with the elbow in extension, whereas stretch of triceps with elbow flexion should
396 provide reciprocal inhibition. Both effects are counter to the observed change from small
397 CMEP with elbow extension to large CMEP with flexion. In contrast, the increase in
398 supraspinal excitability seen with elbow extension is consistent with additional firing of biceps
399 muscle spindle afferents. Previous work shows that increased muscle spindle afferent firing
400 tends to result in larger magnetically-evoked MEPs but has no effect on H reflexes or CMEPs
401 (Stuart et al., 2002), or on MEPs evoked by electrical stimulation, which preferentially activates
402 corticospinal axons directly, bypassing cortical influences to an extent (Kossev et al., 1999).
403 These studies suggest that muscle spindle afferent firing alters cortical excitability more than
404 spinal excitability and supports the differences observed here between MEP/CMEP and CMEP
405 results. Further support for a cortical effect comes from studies showing that changes in
406 shoulder position can modify intracortical facilitation of motor cortical areas supplying upper
407 limb muscles (Ginanneschi et al., 2005; Ginanneschi et al., 2006; Mazzocchio et al., 2008).

408 In Study 2, we investigated the potential contribution of cutaneous stretch receptors to
409 explain posture-dependent changes in motor pathway excitability, but neither CMEPs nor
410 MEPs were changed when cutaneous receptors were activated via skin stretch at a given
411 elbow angle. These results suggest the effect of elbow angle is unlikely to be due to input
412 from cutaneous stretch receptors from skin surrounding the elbow joint. Although the
413 complex skin stretch patterns associated with different elbow angles were not fully replicated,
414 pilot testing revealed that the skin was stretched by similar amounts to, or more than,
415 naturally occurring skin stretch during full elbow flexion or extension. Additionally, similar
416 methodology can induce elbow flexion illusions (Collins et al., 2005), thus it is likely that at
417 least a proportion of the same cutaneous stretch receptors activated by elbow movements are
418 similarly activated by the skin stretch technique used here. While Studies 1 and 2 were
419 performed in different groups of individuals (except for one participant who completed both),
420 arm posture dependent changes in excitability are fairly robust, and have been shown in
421 different participant groups over many studies (Collins & Button, 2018; Collins et al., 2017;
422 Dominici et al., 2005; Forman et al., 2016; Ginanneschi et al., 2005; Ginanneschi et al., 2006;
423 Mazzocchio et al., 2008; Mitsuhashi et al., 2007; Mogk et al., 2014; Nuzzo et al., 2016; Perez
424 & Rothwell, 2015; Peterson et al., 2014; Renner et al., 2006). Therefore, if cutaneous stretch
425 was contributing to changes in excitability with different postures, we would expect such
426 changes to occur in any healthy cohort.

427 If muscle spindle and cutaneous afferent firing do not underlie the spinal level changes
428 in excitability demonstrated by the CMEP, other afferents need to be considered. Autogenic
429 inhibition mediated by Ib afferents from Golgi tendon organs could contribute to stretch-
430 induced changes at more extended angles, though this is unlikely here given that Golgi tendon
431 organs are typically activated during contraction, and autogenic inhibition is relatively short
432 lasting (for review see: Trajano et al., 2017). There may however be a role for heteronymous

433 muscle afferents. Indeed, group I afferents from brachioradialis and pronator teres are shown
434 to exert inhibitory effects on the biceps through oligosynaptic connections with biceps
435 motoneurons (Barry et al., 2008; Naito et al., 1998; Naito et al., 1996). However, these
436 pathways have been identified with manipulations at the proximal radioulnar joint and during
437 weak voluntary contractions. Their role in influencing motoneuronal output in resting muscle
438 and with manipulations of elbow angle remains unknown. Finally, the role of receptors in the
439 joint capsule and ligaments is unexplored.

440 Irrespective of the precise mechanisms involved, CMEPs have a strong monosynaptic
441 component (Petersen et al., 2002), and CMEP changes are likely to reflect changes in the
442 direct corticospinal-motoneuronal pathway. CMEPs are also likely to have some contribution
443 from oligosynaptic connections with motoneurons, such as the propriospinal pathway.
444 However, previous work shows that significant oligosynaptic contributions to the biceps
445 CMEP are only observed when biceps and hand muscles co-contract (Nakajima et al., 2017).
446 Therefore, it is not known whether altered excitability of propriospinal neurones can alter
447 CMEPs in a resting muscle. It is also unknown whether propriospinal neurones have altered
448 excitability or firing related to joint angle that might influence motoneurone excitability at
449 subthreshold levels. Overall, elbow angle dependent differences in CMEP size are likely to
450 reflect the convergence of multiple inhibitory and excitatory inputs to motoneurons, causing
451 a modulation of motoneuronal excitability but the precise mechanism remains unknown.

452 To conclude, a change in elbow angle modifies the size of biceps brachii CMEPs and
453 the MEP/CMEP ratio. A decrease in CMEPs and an increase in the MEP/CMEP ratio at more
454 extended angles suggest decreased spinal-level excitability but an increase in supraspinal
455 excitability. Changes in the MEP/CMEP ratio are potentially due to changes in motor cortical
456 excitability caused by stretch-induced afferent input from muscle spindles but as yet the
457 mechanism to account for the robust changes in CMEPs remains unclear.

458 **Additional information**

459 **Competing Interests**

460 None of the authors have any conflicts of interest.

461

462 **Author Contributions**

463 Experiments were performed at Neuroscience Research Australia, Barker Street, Randwick,
464 Australia. SCD, JLT and JLN contributed to the conception and design of the work, SCD and
465 JLN contributed to the acquisition and analysis of data, SCD, JLT and JLN contributed to the
466 interpretation of data for the work, SCD drafted the manuscript and JLN drafted the figures.
467 SCD, JLT and JLN revised the work critically for important intellectual content.

468 All authors approved the final version of the manuscript and agree to be accountable for all
469 aspects of the work in ensuring that questions related to the accuracy or integrity of any part
470 of the work are appropriately investigated and resolved. All persons designated as authors
471 qualify for authorship, and all those who qualify for authorship are listed.

472

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476

477 **Supporting information**

478 **Supp 1.** Individual data for Figure 3

479 **Supp 2.** Individual data for Figure 4

480

481

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612

613 **Figure captions**

614 **Figure 1.** Experimental setup and protocol. **A)** Electrodes placed over the motor point and
615 distal tendon of biceps brachii recorded electromyographic activity. Transcranial magnetic
616 stimulation (TMS) over the primary motor cortex elicited motor evoked potentials (MEPs),
617 electrical cervicomedullary stimulation elicited cervicomedullary motor evoked potentials
618 (CMEPs) and electrical brachial plexus stimulation elicited maximal compound muscle
619 action potentials (Mmax) in the biceps. For Study 2, pieces of tape with string attached were
620 placed on the skin at various locations near the elbow. The skin was stretched by pulling on
621 the strings and tying them off at hooks on the apparatus. **B)** In Study 1, five elbow angles
622 were tested in random order (full extension (15° (SD 10)), mid extension (50° (SD 5)), 90° ,
623 110° , 130°), and each angle was tested twice. One set of stimuli (5 CMEPs, 1 Mmax and 10
624 MEPs at 0.1 Hz) was delivered each time the angle was changed, so that ten sets of stimuli
625 were delivered in total. For the full extension, 90° and 130° angles, an additional 5 CMEPs
626 matched to the size of MEPs were also elicited per set (0.1 Hz). **C)** In Study 2, three skin
627 stretch conditions were tested in random order with the elbow angle maintained at 90° (skin
628 stretch to mimic full extension, no skin stretch and skin stretch to mimic flexion). Each
629 condition was tested twice. One set of stimuli (5 CMEPs, 10 MEPs and 2 Mmax at 0.1 Hz)
630 was delivered with each change in condition, so that six sets of stimuli were delivered in
631 total.

632

633 **Figure 2.** Averaged Mmax (average of 2 traces), CMEP (average of 10 traces) and MEP
634 (average of 20 traces) traces for a single participant at each of five different elbow angles
635 ranging from 130° of flexion to full extension. For illustrative purposes, dashed lines indicate
636 peak-to-peak amplitudes of responses at full extension. In line with group data, this
637 individual had a decrease in CMEP area as the elbow was placed in more extended positions.
638 This participant had a slightly larger Mmax at full extension in comparison to more flexed
639 positions, also in line with group data. However, this participant had an increase in MEP area
640 with extension, whereas group data revealed no differences in MEP area between angles.

641

642 **Figure 3.** Group data showing the effect of elbow angle on evoked responses (for individual
643 data see Supp 1). **A)** Group data (mean (SD), n = 12) show Mmax areas for each of five
644 different elbow angles ranging from 130° of flexion to full extension (15° (SD 10) of
645 flexion). There was a progressive increase in Mmax as the elbow was placed in more
646 extended positions, with larger Mmax at full extension in comparison to 130° ($p = 0.007$),
647 110° ($p = 0.005$), 90° ($p = 0.019$) and mid extension ($p = 0.028$). **B)** Group data (mean (SD),
648 n = 11) show CMEP (grey bars) and MEP (white bars) areas, normalised to Mmax, for the
649 five different elbow angles. There was a progressive decrease in CMEPs as the elbow was
650 placed in more extended positions, with smaller CMEPs at full extension in comparison to
651 130° ($p = 0.008$), 110° ($p = 0.004$) and 90° ($p = 0.004$). MEP area was not different between
652 angles.

653

654 **Figure 4.** Group data showing the effect of skin stretch on evoked responses (for individual
655 data see Supp 2). **A)** Group data (mean (SD), n = 12) show Mmax areas for three different
656 skin stretch conditions (skin stretch to mimic full extension, no skin stretch and skin stretch to

657 mimic flexion). Mmax was not different between conditions. **B)** Group data (mean (SD),
 658 n = 10) show CMEP (grey bars) and MEP (white bars) areas, normalised to Mmax, for each
 659 skin stretch condition. CMEP and MEP areas were not different between conditions.

660

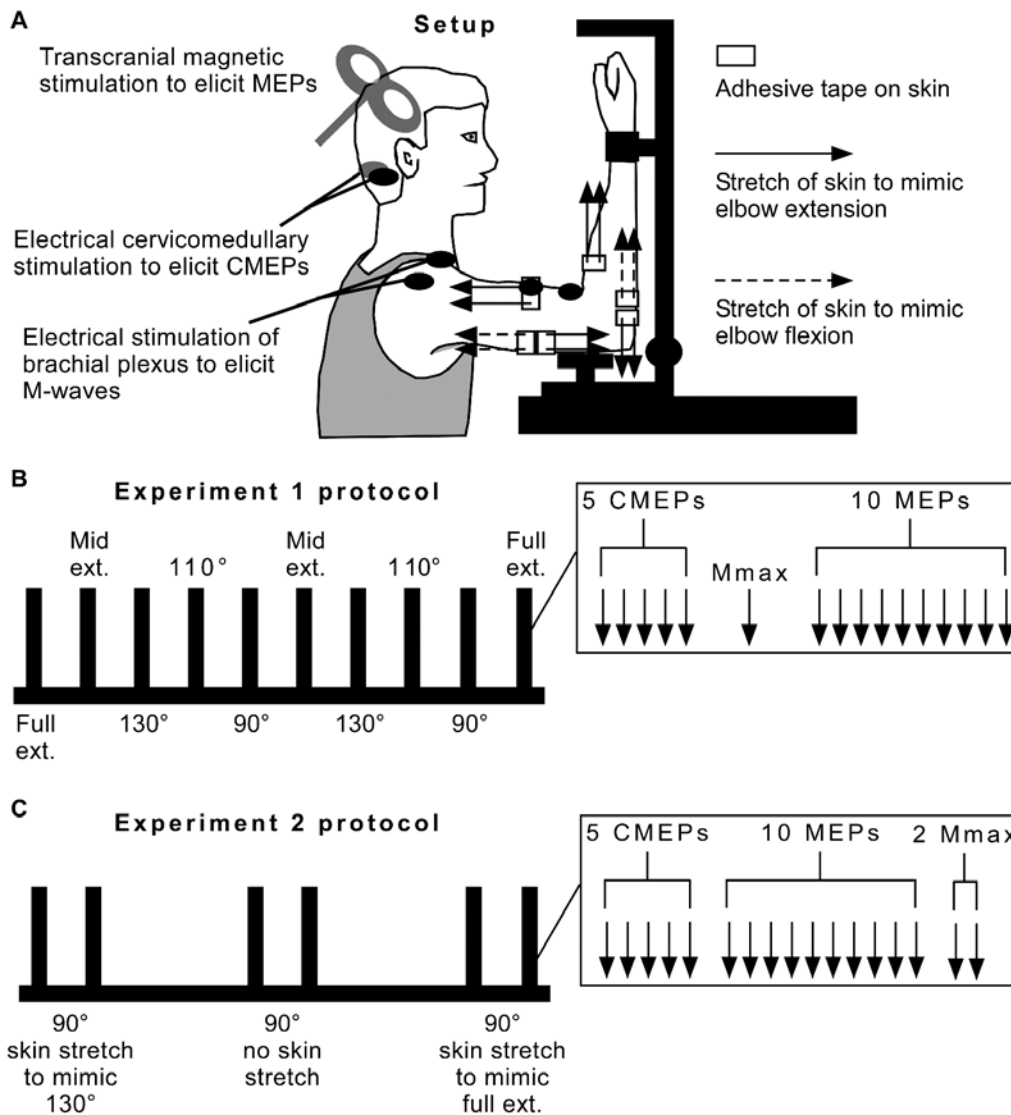
661 **Tables**

662 **Table 1. Amplitudes and areas of biceps brachii evoked potentials in different elbow angle**
 663 **(Study 1) and skin stretch (Study 2) conditions**

Condition	Mmax		CMEP		MEP		Matched CMEP	
	amp	area	amp	area	amp	area	amp	area
Study 1								
130°	13.4 (5.6)	88.5 (35.6)	2.3 (1.0)	11.8 (5.5)	0.5 (0.7)	2.4 (3.6)	0.9 (0.8)	4.3 (4.0)
110°	13.5 (6.1)	90.8 (40.2)	1.8 (1.1)	9.7 (6.3)	0.5 (0.7)	2.7 (4.9)	-	-
90°	15.1 (7.7)	104.5 (46.7)	1.7 (1.0)	9.8 (6.8)	0.5 (0.8)	2.9 (4.8)	0.5 (0.4)	2.4 (2.4)
Mid extension	17.3 (8.0)	123.6 (52.5)	1.3 (1.2)	8.6 (8.2)	0.5 (0.7)	3.4 (4.7)	-	-
Full extension	19.0 (7.9)	134.9 (54.1)	1.3 (1.5)	8.8 (11.3)	0.5 (0.5)	3.2 (3.3)	0.3 (0.3)	1.7 (2.2)
Study 2								
Skin stretch to mimic flexion	16.6 (5.6)	156.4 (56.5)	1.8 (0.8)	12.9 (5.4)	0.9 (0.9)	7.4 (8.0)	-	-
No skin stretch	16.8 (6.1)	157.9 (60.7)	2.2 (1.3)	16.3 (9.7)	0.9 (1.0)	7.9 (9.8)	-	-
Skin stretch to mimic extension	18.5 (6.1)	164.8 (59.4)	2.0 (1.0)	14.0 (6.8)	0.9 (0.6)	7.6 (5.5)	-	-

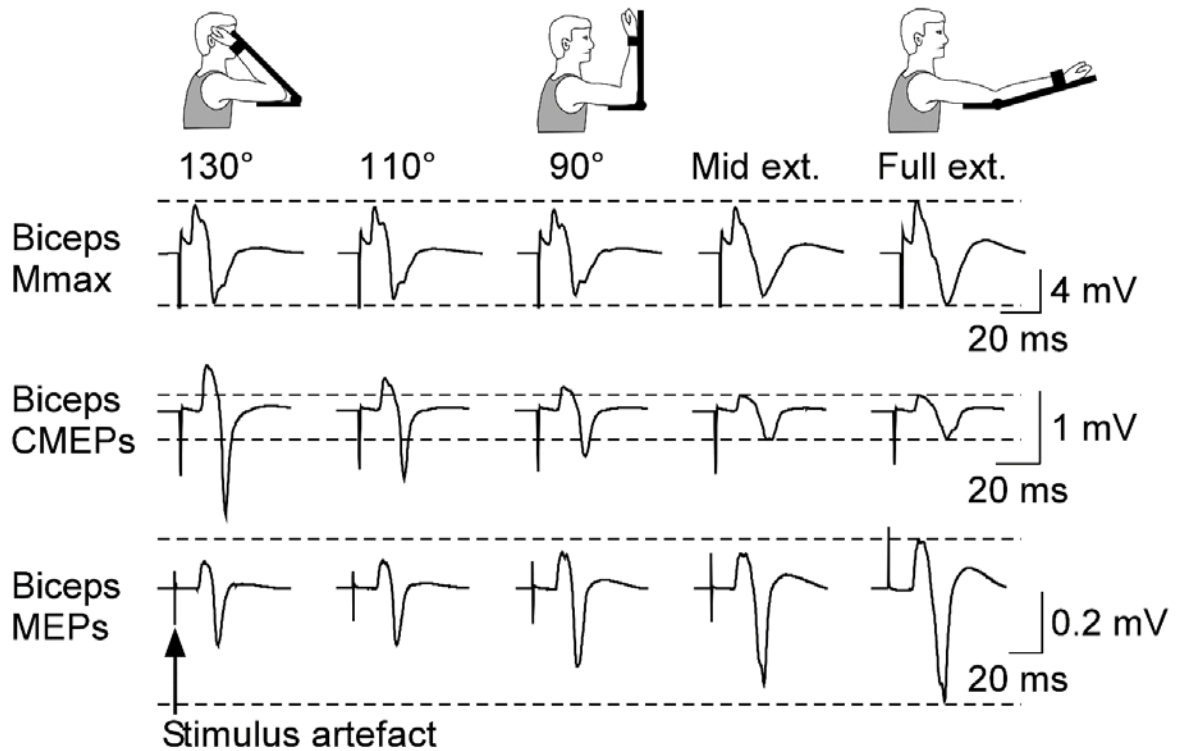
664 Values are peak-to-peak amplitudes (amp; mV) and areas (mV.ms) of biceps brachii evoked
 665 responses given as mean (SD). Mmax: maximal compound muscle action potential; MEP:
 666 motor evoked potential; CMEP: cervicomedullary MEP.

667



668

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 682 stretch conditions were tested in random order with the elbow angle maintained at 90° (skin
 683 stretch to mimic full extension, no skin stretch and skin stretch to mimic flexion). Each
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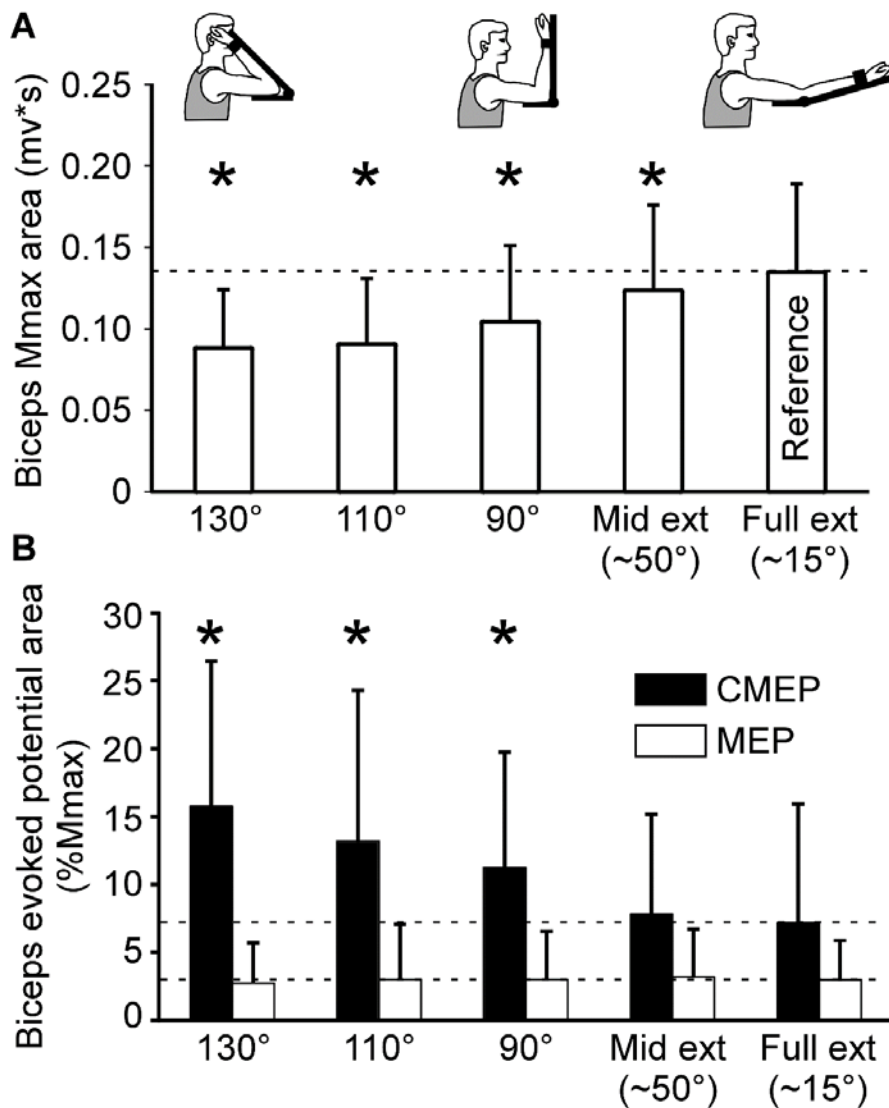
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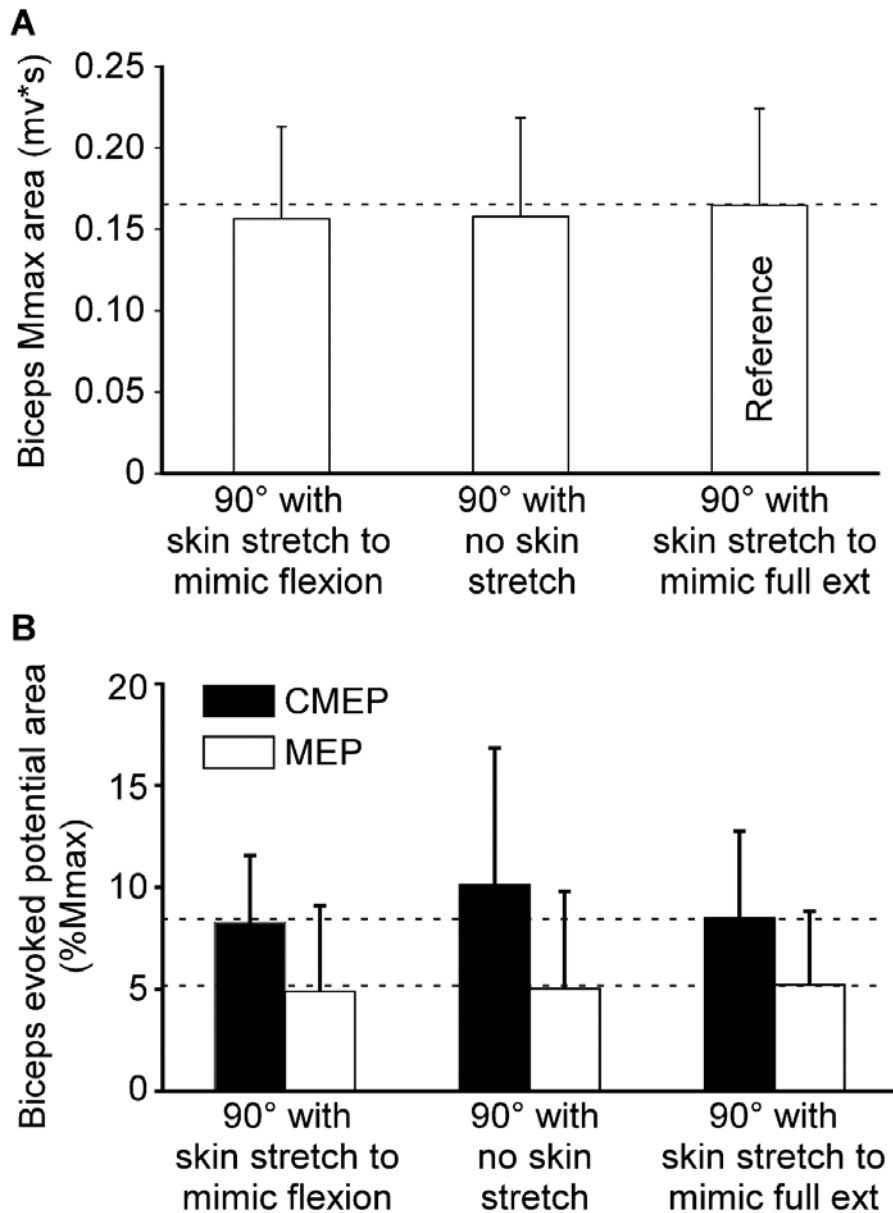
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701

702 **Figure 3.** Group data showing the effect of elbow angle on evoked responses (for individual
 703 data see Supp 1). **A)** Group data (mean (SD), n = 12) show Mmax areas for each of five
 704 different elbow angles ranging from 130° of flexion to full extension (15° (SD 10) of
 705 flexion). There was a progressive increase in Mmax as the elbow was placed in more
 706 extended positions, with larger Mmax at full extension in comparison to 130° ($p = 0.007$),
 707 110° ($p = 0.005$), 90° ($p = 0.019$) and mid extension ($p = 0.028$). **B)** Group data (mean (SD),
 708 n = 11) show CMEP (grey bars) and MEP (white bars) areas, normalised to Mmax, for the
 709 five different elbow angles. There was a progressive decrease in CMEPs as the elbow was
 710 placed in more extended positions, with smaller CMEPs at full extension in comparison to
 711 130° ($p = 0.008$), 110° ($p = 0.004$) and 90° ($p = 0.004$). MEP area was not different between
 712 angles.

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717 **Figure 4.** Group data showing the effect of skin stretch on evoked responses (for individual
 718 data see Supp 2). **A)** Group data (mean (SD), n = 12) show Mmax areas for three different
 719 skin stretch conditions (skin stretch to mimic full extension, no skin stretch and skin stretch to
 720 mimic flexion). Mmax was not different between conditions. **B)** Group data (mean (SD),
 721 n = 10) show CMEP (grey bars) and MEP (white bars) areas, normalised to Mmax, for each
 722 skin stretch condition. CMEP and MEP areas were not different between conditions.

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