Face-hand interactions revealed by afferent inhibition

Electrocutaneous stimulation to the face inhibits motor evoked potentials in the hand: face-hand interactions revealed by afferent inhibition

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25 **Abstract**

26 Reorganization of the sensorimotor cortex following amputation and other
 27 interventions has revealed large-scale plastic changes between the hand and
 28 face representations. To investigate whether hand-face interactions are also
 29 present in the normal state of the system we measured sensorimotor
 30 interactions between these two areas using an afferent inhibition transcranial
 31 magnetic stimulation (TMS) protocol in which the TMS motor evoked potential
 32 (MEP) is inhibited when it is preceded by an afferent stimulus. We hypothesized
 33 that if hand-face interactions exist in the normal state of the system then
 34 stimulation of the face would inhibit hand MEPs. In two separate experiments
 35 we delivered an electrocutaneous stimulus to either the right upper lip
 36 (Experiment 1) or right cheek (Experiment 2) and recorded muscular activity
 37 from the right first dorsal interosseous (FDI). Both lip and cheek stimulation
 38 inhibited FDI MEPs. To investigate the specificity of this effect we conducted
 39 two additional experiments in which cutaneous stimulation was applied to either
 40 the right forearm (Experiment 3) or right arm (Experiment 4). Neither forearm
 41 nor arm stimulation inhibited FDI MEPs. These data provide the first evidence
 42 for face-to-hand afferent inhibition and we suggest that the mechanisms
 43 underlying these sensorimotor interactions could contribute to face/hand
 44 interactions observed following sensorimotor reorganisation.

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50 Introduction

51 The sensory and motor cortices contain somatotopic maps of body areas
 52 and muscles. The medio-lateral organization of these maps is such that the
 53 lower limb is represented medially followed by the trunk, upper limb, and most
 54 laterally the hand and face. The face and hand representations differ from those
 55 of other body parts because their proximity within the maps contrasts starkly
 56 with their separation in the physical body. Furthermore, the extensive area
 57 devoted to processing stimuli or controlling musculature from these two body
 58 parts is disproportionate to their physical size [1,2].

59 The physical proximity of the face and hand within somatosensory and
 60 motor maps is thought to underlie the plasticity that has been documented
 61 following a reduction of sensorimotor inputs from the hand. For example, many
 62 studies have found that amputation or temporary nerve block of the hand
 63 induces an enlargement and shift of the face's sensorimotor representation [3–
 64 7]. This plasticity is paralleled by behavioural changes like referred sensations
 65 in the phantom hand following face stimulation in hand amputees [5,8], phantom
 66 limb pain (Karl et al. 2001), face-hand somatosensory extinction after hand
 67 allograft [9], or improved two-point discrimination in the upper lip after
 68 anaesthesia of hand nerves (median and radial nerves) [4]. While this plasticity
 69 has typically been interpreted as resulting from the reduction of inputs, an
 70 alternative hypothesis posits that it is driven instead by increased input from
 71 other body parts, for example by overuse of the non-amputated hand following
 72 upper-limb amputation [10].

73 In line with the idea that plasticity can also be induced by increased input,
 74 our group has demonstrated in healthy subjects that plasticity between the face

75 and hand is not restricted to instances of reduced input, but can also occur after
76 an *increase* in somatosensory inputs. Using repetitive somatosensory
77 stimulation at the right index finger tip Muret et al. (2014) found improved two-
78 point discrimination at the stimulated fingertip but also on the cheek and upper
79 lip. This “transfer” of behavioural improvement was accompanied by alterations
80 in both hand and face representations in the sensory cortex [12].

81 Face-hand interactions at the somatosensory level are not restricted to
82 situations involving plasticity, but also occur when the system is in its “normal”
83 state. For example, Tanosaki et al., (2003) found that somatosensory evoked
84 magnetic fields induced by electrical stimulation of the thumb were altered when
85 there was concurrent tactile stimulation of the upper face. These findings raise
86 the question of whether face-hand *sensorimotor* interactions might also exist in
87 physiological conditions, in which case they could represent one of the
88 mechanisms underlying both large-scale amputation-induced plasticity as well
89 as temporary, experimentally-induced plasticity, like that observed after
90 repetitive somatosensory stimulation or anaesthesia.

91 We assessed Short-latency Afferent Inhibition (SAI) to test for the
92 existence of face-hand sensorimotor interactions under normal physiological
93 conditions. SAI is the reduction in the amplitude of a muscle response (evoked
94 by TMS of the motor cortex) when motor cortex stimulation is preceded by an
95 afferent stimulus [14–25]. This protocol can provide information about latent
96 sensorimotor interactions between body parts [26–29], and has been widely
97 used to examine sensory interactions *within* the same body part. For example,
98 hand muscle responses are strongly inhibited following stimulation of hand
99 nerves or the skin on the fingertip [14,15,24,25,27,28,16–23], especially when

the stimulus is given close to the target muscle [30], and topographic information can be preserved in the sensory-to-motor inhibitory pattern [31]. Similarly, stimulation of the shoulder area inhibits responses in the shoulder muscle infraspinatus [32], and stimulation of the dorsal surface of the foot inhibits responses in the leg muscle tibialis anterior [29]. Afferent inhibition can also occur when the muscle of interest and the sensory stimulation site are within the same body part but anatomically separate. For example, stimulation of the index fingertip inhibits various muscles of the arm and forearm on the same side as the fingertip stimulation [28], and can also inhibit hand muscles on the opposite side of the body [29].

To date, there is no evidence for the existence of SAI between body parts, although the only combinations examined have been the lower and upper limbs [28]. Here we investigated if and when SAI exists between the face and the hand, as it is known that these anatomically distant body parts have strong interactions both under normal physiological conditions and following a plasticity-inducing manipulation. SAI is typically considered to occur at a latency related to the delay of arrival of the afferent information at the motor cortex. For example, following fingertip stimulation, maximal inhibition is observed between 25 and 35 ms. This assumption is based upon within-body part SAI, however, there are currently no data indicating whether a similar rule applies for SAI between body parts. Furthermore, the results of the only study that investigated SAI within the face suggest that face stimulation might not follow this same rule, as there was some evidence of face-face SAI at 30ms but none at shorter (expected) ISIs [22]. Thus, the aim of the experiments presented here was to 1) establish **if and when** afferent inhibition exists between two anatomically

125 separate body parts: the face and the hand; and 2) whether this between body-
126 part inhibition is specific to the face and the hand or is also present between the
127 forearm or upper-arm and the hand.

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129

130 **Materials and Methods**

131 **Participants**

132 Forty-four healthy right-handed volunteers were included in four separate
133 experiments. It is important to note that each experiment was independent of
134 the others, as the aim of this study was to investigate if and when SAI exists
135 between a given body part and the right FDI, not to compare the amount or
136 latency of SAI between the four stimulated sites. Fourteen individuals
137 participated in Experiment 1 (mean age of 22.7 ± 7.1 years, 5 males), 12 in
138 Experiment 2 (mean age of 23.7 ± 6.7 years, 3 males), 15 in Experiment 3
139 (mean age of 25.5 ± 6.4 years, 2 males) and 13 in Experiment 4 (mean age of
140 24.8 ± 3.9 years, 3 males). Four subjects participated in two experiments (1 & 2
141 (n=2); 1 & 3 (n=1); 3 & 4 (n=1)) and 3 subjects participated in 3 experiments (1,
142 2 & 3 (n=1); 1, 3 & 4 (n=1); 2, 3 & 4 (n=1)). All participants gave written
143 informed consent. The protocol was approved by the ethical committees of the
144 Grenoble University Hospital (ID RCB: 2016-A01668-43) and the *Comité de*
145 *protection des personnes* (CPP) SUD EST IV (ID RCB: 2010-A01180-39) and
146 conformed to the ethical aspects of the Declaration of Helsinki.

147

148 **General experimental procedures**

149 In each of the four experiments participants were comfortably seated with
150 their arm resting on an armrest (elbow flexed at 90°) and a single tactile
151 electrical stimulus was applied prior to a single transcranial magnetic stimulation
152 pulse over the hand area of the left motor cortex. The tactile stimulus was
153 applied to the right upper lip (Experiment 1), right cheek (Experiment 2), right
154 forearm (Experiment 3), or right arm (Experiment 4). In all four experiments
155 electromyographic activity was recorded from the right first dorsal interosseous
156 (FDI) and the inter-stimulus intervals (ISIs) between the electrocutaneous
157 stimulus and the TMS pulse were 15, 25, 35, 45, 55, 65, 75 and 85 ms. In all
158 four experiments 14 trials of each ISI plus 34 TMS-only trials were presented in
159 a random order with an inter-trial interval between 5 and 8 seconds. Every 24
160 trials the experiment was paused to give a short break to the participant.
161 Experiments 1 and 2 were conducted in the IMPACT team (Lyon, France) and
162 Experiments 3 and 4 in the IRMaGe MRI and Neurophysiology facilities
163 (Grenoble, France).

164

165 **Electrical Stimulation**

166 Single pulse electrocutaneous stimuli (square wave, 200 μ s) were
167 delivered via a constant current stimulator (DS7A, Digitimer Ltd, UK) using
168 bipolar adhesive electrodes (Neuroline 700, Ambu, Copenhagen, Denmark)
169 placed on the face (Experiments 1 & 2) or the upper limb (Experiments 3 & 4).
170 The sensory perception threshold (SPT) for each stimulation site was
171 determined as the minimum stimulation intensity at which the subject reported
172 feeling the stimulation on 2 out of 3 trials. Sensory afferent inhibition protocols
173 always use non-painful stimuli and typically use intensities between 2 and 3

174 times SPT [14,26,28,31,33]. Tamburin et al. (2001) showed that stimulation
175 applied to the tip of the little finger at 3xSPT produced inhibition in abductor
176 digiti minimi comparable to that recorded at 5xSPT, and Bikmullina et al. (2009)
177 showed that when stimulation was applied to the index finger inhibition in arm
178 and forearm muscles was greater at 3xSPT than at 1x or 2x. The
179 electrocutaneous stimulus intensities used in each experiment are shown in
180 Table 1 and the Kruskal-Wallis test by ranks revealed no difference between the
181 absolute stimulus intensity used in each of the four experiments ($p=0.15$).

182

183 **Table 1. Average electrocutaneous and TMS stimulus intensities used in**
184 **each of the four experiments, plus average TMS-only amplitude of FDI**
185 **MEPs (mean $\pm$ SEM).**

Exp.	ES location	ES intensity (mA)	rMT (%MSO)	1mV intensity (%MSO)	TMS-only (mV)
1	Upper Lip	4.1 $\pm$ 0.5	40 $\pm$ 1.0	44 $\pm$ 2.0	0.9 $\pm$ 0.1
2	Cheek	5.0 $\pm$ 0.4	39 $\pm$ 0.1	43 $\pm$ 0.2	1.0 $\pm$ 0.2
3	Forearm	4.6 $\pm$ 0.2	45 $\pm$ 3.6	57 $\pm$ 4.6	1.1 $\pm$ 0.1
4	Arm	4.1 $\pm$ 0.3	47 $\pm$ 2.8	59 $\pm$ 3.6	1.1 $\pm$ 0.1

186 ES: Electrocutaneous Stimulation; rMT: resting Motor Threshold; MSO:
187 Maximum Stimulator Output; TMS-only: FDI MEP amplitude in the absence of
188 electrocutaneous stimulation.

189

190 **Experiment 1: SAI between the right upper lip and the right FDI**

191 Two electrodes were placed side-by-side horizontally, separated by 1
192 cm, over the right upper lip with the more medial electrode close to the philtral

ridge. Stimulation was delivered at 2xSPT because higher intensities were reported as painful in the majority of subjects.

195

196 **Experiment 2: SAI between the right cheek and the right FDI**

Two electrodes were placed 1 cm apart vertically, at the approximate midpoint between the right ear and the right corner of the mouth. As for the upper-lip, stimulation was delivered at 2xSPT because higher intensities were reported as painful in the majority of subjects.

201

202 **Experiment 3: SAI between the right forearm and the right FDI**

Electrodes were placed 1 cm apart on the anterolateral face of the forearm in the middle of the proximal third of the forearm on the skin overlying the extensor carpi radialis. Stimulation was delivered at 3xSPT.

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207 **Experiment 4: SAI between the right arm and the right FDI**

Electrodes were placed 1.5 cm apart on the medial face of the arm in the middle of the proximal third of the upper arm on the skin overlying the border between the biceps and the triceps. As for the forearm, the stimulation was delivered at 3xSPT.

212

213 **Transcranial magnetic stimulation (TMS) and** 214 **electromyography (EMG)**

TMS was applied over the left motor cortex and EMG activity was recorded from the right FDI via surface electrodes (DE-2.1, Delsys,

Massachusetts, USA) placed on the muscle belly. EMG activity was recorded at 2000 Hz, digitized (Power 1401II, Cambridge Electronics Design, Cambridge, UK) and stored on a computer for off-line analysis (Spike 2 or Signal, Cambridge Electronics Design, Cambridge, UK). In Experiments 1 and 2 TMS was applied using a 9 cm figure-of-eight coil and a Magstim 200 stimulator (Magstim, Carmarthenshire, UK). In Experiments 3 and 4 TMS was applied using a 7.5 cm figure of eight coil and a MagPro x100 stimulator (Magventure, Skovlunde, Denmark).

The coil was positioned over the hand area of the primary motor cortex and the optimal point for stimulating FDI was found by stimulating at a slightly suprathreshold intensity and identifying the point with the largest, most stable responses. To enable the experimenter to accurately maintain the coil over the optimal position throughout the experiment this point was recorded in a neuro-navigation system (Brainsight, Rogue Resolutions, Cardiff, UK (Experiments 1 & 2), Localite neuronavigation system, Localite GmbH, Sankt Augustin, Germany (Experiments 3 & 4)). The resting Motor Threshold (rMT) was determined as the minimum stimulator intensity necessary to evoke MEPs of at least 50 μ V (peak-to-peak amplitude) on at least 5 out of 10 trials. The TMS pulse intensity used during the experiment was adjusted to produce MEPs in the control condition (TMS-only) with a mean amplitude of approximately 1mV. The average rMT and intensity that produced a MEP of approximately 1mV (both expressed as a percentage of the maximum stimulator output (%MSO)) are shown separately for each experiment in Table 1. A Kruskal-Wallis test revealed no difference between the amplitude of the TMS-only MEPs in each of the four experiments ($p = 0.46$).

242 Throughout the experiment, the baseline EMG signal was constantly
243 monitored to ensure that the muscle was completely relaxed. If muscle activity
244 was detected the subject received a verbal instruction to relax the hand. Trials
245 contaminated by muscle contraction in the 500ms before the TMS pulse were
246 excluded from further analyses.

247

248 **Statistical analysis**

249 Data from each of the four experiments were analysed separately. Peak-
250 to-peak MEP amplitudes (mV) were measured off-line using custom-written
251 Spike 2 or Signal scripts (Cambridge Electronics Design, Cambridge, UK).
252 Trials were excluded if they were contaminated by muscle contraction or if their
253 amplitudes were greater than or less than 1.96 SDs from the mean of that
254 condition for that subject. On average 16 ($\pm$ 1.1 SEM) trials were excluded for
255 each subject. The mean MEP amplitude for each condition was then calculated.
256 D'Agostino-Pearson omnibus tests were applied to verify if the data came from
257 an approximately normal distribution. Since the data for some conditions were
258 not normally distributed, a Friedman repeated measures, non-parametric rank
259 test with one factor (ISI) was applied to the raw MEP amplitudes (mV) to
260 compare the mean amplitudes across conditions. Dunn's Multiple Comparison
261 post-hoc tests comparing the control condition (TMS-only) with each ISI (15 to
262 85ms) were applied if the factor ISI was significant with a significance level of
263 0.05. Data were analysed using Prism 5 (GraphPad Software, Inc., California,
264 USA). For each subject, mean MEP amplitude values for each ISI were
265 normalized to the mean of the TMS-only condition and these normalized data

were used to graphically represent the results but all analyses were conducted on raw MEP amplitudes.

Results

Hand muscle inhibition following electrocutaneous stimulation on the face

Experiment 1

Fig 1A shows that electrocutaneous stimulation of the right upper lip inhibited right FDI MEPs by between 20 and 30% at the 45, 55, and 65ms ISIs. A Friedman test on the mean MEP amplitude for each subject in each condition revealed a significant main effect of ISI ($\chi^2(8) = 21.20$; $p = 0.007$). Dunn's post-hoc tests comparing the mean MEP amplitude at each ISI against the mean TMS-only MEP amplitude revealed that inhibition was significant only at the 45ms ISI.

Fig 1. Normalized mean MEP amplitudes in the right FDI after electrocutaneous stimulation of the right upper lip – Experiment 1 (A), right cheek – Experiment 2 (B), right forearm – Experiment 3 (C) and right arm – Experiment 4 (D). Bars represent the standard error of the mean. The black dashed lines represent the TMS-only MEP amplitude. Asterisks represent significant Dunn's post-hoc tests ($p < 0.05$) comparing mean TMS-only amplitude with mean amplitude at each ISI. Note that statistical tests were performed on non-normalized data (S1 Appendix).

290

291 **Experiment 2**

292 Fig 1B shows that electrocutaneous stimulation of the right cheek
 293 produced a similar pattern and amount of inhibition as lip stimulation (between
 294 20 and 30% at the 45, 55, and 65ms ISIs). A Friedman test on the mean MEP
 295 amplitude for each subject in each condition revealed a significant main effect of
 296 ISI ($\chi^2 (8) = 16.44$; $p = 0.036$). Dunn's post-hoc tests comparing the mean MEP
 297 amplitude at each ISI against the mean TMS-only MEP amplitude revealed that
 298 this inhibition was significant only at the 55ms ISI.

299

300 **Hand muscle inhibition following electrocutaneous** 301 **stimulation on the arm**

302 **Experiment 3**

303 Fig 1C shows that electrocutaneous stimulation of the right forearm
 304 inhibited right FDI MEPs by between 10 and 20% at the 25 and 55ms ISIs. A
 305 Friedman test on the mean MEP amplitude for each subject in each condition
 306 revealed no main effect of ISI ($\chi^2 (8) = 8.34$; $p = 0.401$).

307

308 **Experiment 4**

309 Fig 1D shows that electrocutaneous stimulation of the right arm also
 310 inhibited FDI MEPs by between 10 and 20% at the 35 to 65ms ISIs, but similar
 311 to the forearm, a Friedman test on the mean MEP amplitude for each subject in
 312 each condition revealed no main effect of ISI ($\chi^2 (8) = 8.96$; $p = 0.345$).

313

314

315 **Discussion**

316 **Face stimulation can inhibit hand MEPs**

317 Face-hand sensorimotor interactions are clearly important for feeding,
 318 grooming, non-verbal communication and many other activities of daily life [34].
 319 These interactions exist at a fundamental level in the nervous system in the
 320 form of reflexes. For example, the Babkin reflex in neonates occurs when palm
 321 pressure evokes mouth opening [35], and the palmomenta reflex occurs in
 322 adults when thenar eminence stimulation evokes contraction of the mentalis
 323 muscle of the chin [36]. Higher-order face-hand interactions have also been
 324 documented under situations of plasticity, but evidence for non-reflexive
 325 interactions under normal, physiological conditions in the adult is rare. Here, we
 326 present the first evidence of sensorimotor afferent inhibitory interactions
 327 between the face and the hand. We found that electrocutaneous stimulation of
 328 the right upper lip (Experiment 1) and right cheek (Experiment 2) significantly
 329 inhibited MEP amplitudes in the right FDI. Interestingly, this between body part
 330 SAI appears to be specific to the face and the hand, as despite being
 331 anatomically closer to the FDI, forearm (Experiment 3) and arm (Experiment 4)
 332 stimulation did not alter the amplitude of FDI MEPs.

333 These results provide the first evidence for sensorimotor afferent
 334 inhibitory interactions between the face and the hand. These findings reinforce
 335 the idea that there are privileged interactions between the face and the hand
 336 and that such interactions are not limited to reflexes or situations in which the
 337 system is perturbed.

338 The temporal dynamics with which touch on the face inhibited hand
339 muscle responses suggest that face-hand afferent inhibition mechanisms differ
340 from those underlying hand-hand inhibition. For example, most studies
341 examining fingertip or median nerve stimulation show that inhibition of hand
342 muscle MEPs begins just after the arrival of the afferent volley in the primary
343 somatosensory cortex (S1) – at an ISI of approximately 25ms [14,23,27,28].
344 Many studies even use electroencephalography to measure the latency of this
345 afferent volley and then choose their sensory-TMS ISIs so that the TMS pulse
346 arrives at the time when the sensory information is presumed to have been
347 transferred to the motor cortex i.e. several milliseconds after the arrival of the
348 afferent volley in S1 [20,21,37–40]. This technique is based upon the
349 hypothesis that afferent inhibition results from the activation of direct inhibitory
350 connections from the primary sensory to primary motor cortices. If face-hand
351 afferent inhibition were based upon the same mechanisms as hand-hand
352 afferent inhibition we would have observed it around 15ms, not 45 or 55 ms
353 [41,42]. Interestingly, in a study of face-face afferent inhibition, Pilurzi et al.,
354 (2013) found no statistically significant inhibition, but visual inspection of their
355 results (see Fig 5, page 1898) suggests that some inhibition might be present
356 around 30ms – later than would be expected based upon the arrival of the
357 afferent volley in S1 - but similar to the delay we observed for inhibition between
358 the face and the hand. This suggests that the ISIs at which we observed
359 significant face-hand inhibition might not be attributable to the fact that the AI
360 was between two body parts, but might instead be a feature of AI involving face
361 stimulation.

When a somatosensory stimulus arrives in the S1 cortex, it evokes a series of positive (P) and negative (N) deflections. Face stimulation evokes somatosensory evoked potentials (SEPs for EEG) or somatosensory evoked fields (SEFs for MEG) between 15ms (N15) and 65ms (P65) [41–45]. Other deflections are also measurable at longer latencies (70-120ms), and these are thought to reflect later stages of somatosensory processing within the secondary somatosensory cortices [45–47]. The posterior parietal cortex also plays a role in this later processing, starting at approximately 90ms for upper limb stimulation [46,48]. Our finding of significant face-hand inhibition at ISIs of 45 and 55 ms suggests that afferent information from the face alters hand motor representations during early somatosensory processing, albeit at a relatively advanced stage of early processing. Indeed, since we observed face-hand inhibition before 70ms it likely involves S1, and despite being later than hand-hand inhibition, still reflects the phenomenon of short-latency afferent inhibition. Had it occurred at longer ISIs (closer to 100ms) we would have suggested that the inhibition reflected long-latency afferent inhibition and relied upon late somatosensory processing involves structures such as bilateral secondary somatosensory cortices and contralateral posterior parietal cortex [16,17,19,22,25].

381

382 **Arm and Forearm stimulation does not inhibit hand** 383 **MEPs**

The majority of afferent inhibition studies have focused on the upper and lower limbs, either looking at interactions within the same part of the limb (hand-hand [14–16,18,19,23,24,27,28], shoulder-shoulder [32], leg-leg [49], or

387 between different limb segments (hand-arm, hand-forearm [26–28], foot-leg
388 [29]). On the basis of these studies, it is generally believed that afferent
389 inhibition within the upper limb is a robust phenomenon. Interestingly, however,
390 we are only aware of one other investigation of afferent inhibition between
391 different parts of the upper limb in which stimulation was not applied to the hand
392 [28]. As in our study, they observed no inhibition in hand (and other) muscles
393 following forearm stimulation at 3xSPT. Thus, it would appear that inhibition
394 within the upper limb is not as robust as previously thought, and instead is
395 present only when the afferent stimulation is on or near the hand.

396 One possible explanation for the absence of arm-hand afferent inhibition
397 might be that the higher sensitivity and larger cortical magnification of the hand
398 [1,2,50] leads to a larger cortical response to hand stimulation than to forearm
399 or arm stimulation. We believe this to be unlikely, however, as a stimulus on the
400 arm five times longer than that used in the present study still failed to inhibit
401 hand muscle responses [28]. Given our finding of face-hand inhibition, it is
402 important that future studies continue to investigate if and when arm-hand
403 inhibition can be evoked.

404 The inhibitory interaction between the face and hand revealed here might
405 constitute one of the sources of face-hand cortical interactions like those
406 observed after plasticity-inducing events [3,4,9]. As initially suggested by
407 Jacobs and Donoghue (1991), one possible mechanism of cortical
408 reorganization is the unmasking of pre-existing lateral excitatory connections by
409 the reduction of activity in intracortical inhibitory circuits. The inhibitory
410 sensorimotor interaction observed here might contribute to maintaining
411 functional boundaries between face and hand cortical territories. After a

412 plasticity-inducing event (e.g. deafferentation), activity in the inhibitory circuitry
413 could be decreased, resulting in the disinhibition of latent intracortical excitatory
414 connections and a reduction in SAI, as shown by Bailey et al., (2015) in patients
415 with spinal cord injury. Another possibility is that the face-hand sensorimotor
416 inhibitory interactions reported here are one of the potential physiological
417 substrates upon which a multitude of remotely represented body parts may
418 enter a (missing) hand territory based upon the frequency of usage of these
419 body parts [10,53,54]. Were this case, however, we should also have found AI
420 between the arm and the hand.

421 In spite of increasing interest in afferent inhibition, its underlying function
422 remains unknown (reviewed in Turco et al., 2017). Some studies use it as a tool
423 to investigate the integrity of the cholinergic system [20,56], while others use it
424 as we did here: as a tool to probe sensorimotor interactions in neurologically
425 healthy individuals [15,16,22,24,25]. Participants in these studies are always
426 seated quietly and never perform any particular task. The experiments
427 presented in this paper constitute the first step in investigating the existence of
428 SAI between the face and the hand as the ISIs at which it is present. In the
429 future, it will be interesting to directly compare the amount and latency of SAI at
430 various body sites within the same participants, as well as to examine whether
431 the face hand interactions demonstrated here are altered as a function of the
432 proximity of the two body parts and/or their engagement in hand-to-mouth
433 behaviours. These types of experiments will not only shed more light on face-
434 hand afferent inhibition, but could also help us to better understand the
435 functional importance of the sensorimotor interactions that underlie afferent
436 inhibition.

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439 **Acknowledgements**

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441 **References**

- 442 1. Penfield W, Boldrey E. Somatic Motor and Sensory Representation in the
443 Cerebral Cortex of Man as Studied by Electrical Stimulation. Brain. 1937;
444 389–443. doi:10.1093/brain/60.4.389
- 445 2. Nakamura A, Yamada T, Goto A, Kato T, Ito K, Abe Y, et al.
446 Somatosensory Homunculus as Drawn by MEG. Neuroimage. 1998;7:
447 377–386. doi:10.1006/nimg.1998.0332
- 448 3. Raffin E, Richard N, Giraux P, Reilly KT. Primary motor cortex changes
449 after amputation correlate with phantom limb pain and the ability to move
450 the phantom limb. Neuroimage. 2016;130: 134–144.
451 doi:10.1016/j.neuroimage.2016.01.063
- 452 4. Weiss T, Miltner WHR, Liepert J, Meissner W, Taub E. Rapid functional
453 plasticity in the primary somatomotor cortex and perceptual changes after
454 nerve block. Eur J Neurosci. 2004;20: 3413–3423. doi:10.1111/j.1460-
455 9568.2004.03790.x
- 456 5. Ramachandran VS. Behavioral and magnetoencephalographic correlates
457 of plasticity in the adult human brain. Proc Natl Acad Sci U S A. 1993;90:
458 10413–10420.
- 459 6. Flor H, Elbert T, Knecht S, Wienbruch C, Pantev C, Birbaumer N, et al.
460 Phantom-limb pain as a perceptual correlate of cortical reorganization

- 461 following arm amputation. *Nature*. 1995;375: 482–484.
462 doi:10.1038/375482a0
- 463 7. Pascual-Leone A, Peris M, Tormos JM, Pascual-Leone Pascual A, Catalá
464 MD. Reorganization of Human Cortical Motor Output Maps Following
465 Traumatic Forearm Amputation. *Neuroreport*. 1996;7: 2068–2070.
- 466 8. Halligan PW, Marshall JC, Wade DT, Davey J, Morrison D. Thumb in
467 cheek? Sensory reorganization and perceptual plasticity after limb
468 amputation. *Neuroreport*. 1993;4: 233–6. doi:10.1097/00001756-
469 199303000-00001
- 470 9. Farnè A, Roy AC, Giroux P, Pawson T, Sirigu A. Face or hand, not both:
471 Perceptual correlates of reafferentation in a former amputee. *Curr Biol*.
472 2002;12: 1342–1346. doi:10.1016/S0960-9822(02)01018-7
- 473 10. Makin TR, Cramer AO, Scholz J, Hahamy A, Slater DH, Tracey I, et al.
474 Deprivation-related and use-dependent plasticity go hand in hand. *Elife*.
475 2013;2: 1–15. doi:10.7554/eLife.01273
- 476 11. Muret D, Dinse HR, Macchione S, Urquizar C, Farnè A, Reilly KT. Touch
477 improvement at the hand transfers to the face. *Curr Biol*. Elsevier;
478 2014;24: R736–R737. doi:10.1016/j.cub.2014.07.021
- 479 12. Muret D, Daligault S, Dinse HR, Delpuech C, Mattout J, Reilly KT, et al.
480 Neuromagnetic correlates of adaptive plasticity across the hand-face
481 border in human primary somatosensory cortex. *J Neurophysiol*.
482 2016;115: 2095–2104. doi:10.1152/jn.00628.2015
- 483 13. Tanosaki M, Iguchi Y, Hoshi Y, Hashimoto I. Tactile interference to the
484 face affects magnetic responses elicited by electric thumb stimulation.
485 *Clin Neurophysiol*. 2003;114: 2118–2123. doi:10.1016/S1388-

- 486 2457(03)00239-6
- 487 14. Tokimura H, Di Lazzaro V, Tokimura Y, Oliviero A, Profice P, Insola A, et
- 488 al. Short latency inhibition of human hand motor cortex by somatosensory
- 489 input from the hand. *J Physiol.* 2000;523: 503–513. Available:
- 490 <http://www.jphysiol.org/cgi/content/abstract/523/2/503>
- 491 15. Tamburin S, Manganotti P, Zanette G, Fiaschi a. Cutaneomotor
- 492 integration in human hand motor areas: Somatotopic effect and
- 493 interaction of afferents. *Exp Brain Res.* 2001;141: 232–241.
- 494 doi:10.1007/s002210100859
- 495 16. Chen R, Corwell B, Hallett M. Modulation of motor cortex excitability by
- 496 median nerve and digit stimulation. *Exp Brain Res.* 1999;129: 77–86.
- 497 doi:10.1007/s002210050938
- 498 17. Kukaswadia S, Wagle-Shukla A, Morgante F, Gunraj C, Chen R.
- 499 Interactions between long latency afferent inhibition and interhemispheric
- 500 inhibitions in the human motor cortex. *J Physiol.* 2005;563: 915–924.
- 501 doi:10.1113/jphysiol.2004.080010
- 502 18. Sailer A, Molnar GF, Cunic DI, Chen R. Effects of peripheral sensory
- 503 input on cortical inhibition in humans. *J Physiol.* 2002;544: 617–29.
- 504 doi:10.1113/jphysiol.2002.028670
- 505 19. Sailer A, Molnar GF, Paradiso G, Gunraj CA, Lang AE, Chen R. Short
- 506 and long latency afferent inhibition in Parkinson’s disease. *Brain.*
- 507 2003;126: 1883–1894. doi:10.1093/brain/awg183
- 508 20. Di Lazzaro V, Oliviero A, Tonali PA, Marra C, Daniele A, Profice P, et al.
- 509 Noninvasive in vivo assessment of cholinergic cortical circuits in AD using
- 510 transcranial magnetic stimulation. *Neurology.* 2002;59: 392–397.

- doi:10.1212/WNL.59.3.392
21. Di Lazzaro V, Pilato F, Dileone M, Tonali PA, Ziemann U. Dissociated effects of diazepam and lorazepam on short-latency afferent inhibition. *J Physiol.* 2005;569: 315–323. doi:10.1113/jphysiol.2005.092155
22. Pilurzi G, Hasan a, Saifee T a, Tolu E, Rothwell JC, Deriu F. Intracortical circuits, sensorimotor integration and plasticity in human motor cortical projections to muscles of the lower face. *J Physiol.* 2013;591: 1889–906. doi:10.1113/jphysiol.2012.245746
23. Asmussen MJ, Jacobs MF, Lee KGH, Zapallow CM, Nelson AJ. Short-Latency Afferent Inhibition Modulation during Finger Movement. *PLoS One.* 2013;8: e60496. doi:10.1371/journal.pone.0060496
24. Asmussen MJ, Zapallow CM, Jacobs MF, Lee KGH, Tsang P, Nelson AJ. Modulation of short-latency afferent inhibition depends on digit and task-relevance. *PLoS One.* 2014;9: e104807. doi:10.1371/journal.pone.0104807
25. Lapole T, Tindel J. Acute effects of muscle vibration on sensorimotor integration. *Neurosci Lett.* Elsevier Ireland Ltd; 2015;587: 46–50. doi:10.1016/j.neulet.2014.12.025
26. Tamburin S, Fiaschi A, Andreoli A, Marani S, Zanette G. Sensorimotor integration to cutaneous afferents in humans: the effect of the size of the receptive field. *Exp Brain Res.* 2005;167: 362–9. doi:10.1007/s00221-005-0041-y
27. Helmich RCG, Bäumer T, Siebner HR, Bloem BR, Münchau A. Hemispheric asymmetry and somatotopy of afferent inhibition in healthy humans. *Exp Brain Res.* 2005;167: 211–219. doi:10.1007/s00221-005-

- 536 0014-1
- 537 28. Bikmullina R, Bäumer T, Zittel S, Münchau A. Sensory afferent inhibition
538 within and between limbs in humans. Clin Neurophysiol. International
539 Federation of Clinical Neurophysiology; 2009;120: 610–618.
540 doi:10.1016/j.clinph.2008.12.003
- 541 29. Ruddy KL, Jaspers E, Keller M, Wenderoth N. Interhemispheric
542 sensorimotor integration; an upper limb phenomenon? Neuroscience. The
543 Authors; 2016;333: 104–113. doi:10.1016/j.neuroscience.2016.07.014
- 544 30. Dubbioso R, Raffin E, Karabanov A, Thielscher A, Siebner HR. Centre-
545 surround organization of fast sensorimotor integration in human motor
546 hand area. Neuroimage. Elsevier Ltd; 2017;158: 37–47.
547 doi:10.1016/j.neuroimage.2017.06.063
- 548 31. Tamè L, Pavani F, Braun C, Salemme R, Farnè A, Reilly KT. Somatotopy
549 and temporal dynamics of sensorimotor interactions: Evidence from
550 double afferent inhibition. Eur J Neurosci. 2015;41: 1459–1465.
551 doi:10.1111/ejn.12890
- 552 32. Bradnam L, Shanahan EM, Hendy K, Reed A, Skipworth T, Visser A, et
553 al. Afferent inhibition and cortical silent periods in shoulder primary motor
554 cortex and effect of a suprascapular nerve block in people experiencing
555 chronic shoulder pain. Clin Neurophysiol. International Federation of
556 Clinical Neurophysiology; 2016;127: 769–778.
557 doi:10.1016/j.clinph.2015.03.012
- 558 33. Tamburin S, Manganotti P, Marzi CA, Fiaschi A, Zanette G. Abnormal
559 somatotopic arrangement of sensorimotor interactions in dystonic
560 patients. Brain. 2002;125: 2719–2730. doi:10.1093/brain/awf279

- 561 34. Rochat P. Chapter 10 Hand-Mouth Coordination in The Newborn:
562 Morphology, Determinants, and Early Development of A Basic Act.
563 Advances in Psychology. 1993. pp. 265–288. doi:10.1016/S0166-
564 4115(08)60956-5
- 565 35. Futagi Y, Yanagihara K, Mogami Y, Ikeda T, Suzuki Y. The Babkin reflex
566 in infants: Clinical significance and neural mechanism. *Pediatr Neurol*.
567 2013;49: 149–155. doi:10.1016/j.pediatrneurol.2013.04.005
- 568 36. Boes CJ. The history of examination of reflexes. *J Neurol*. 2014;261:
569 2264–2274. doi:10.1007/s00415-014-7326-7
- 570 37. Alle H, Heidegger T, Kriváneková L, Ziemann U. Interactions between
571 short-interval intracortical inhibition and short-latency afferent inhibition in
572 human motor cortex. *J Physiol*. 2009;587: 5163–5176.
573 doi:10.1113/jphysiol.2009.179820
- 574 38. Cash RFH, Isayama R, Gunraj CA, Ni Z, Chen R. The influence of
575 sensory afferent input on local motor cortical excitatory circuitry in
576 humans. *J Physiol*. 2015;593: 1667–84.
577 doi:10.1113/jphysiol.2014.286245
- 578 39. Fischer M, Orth M. Short-latency sensory afferent inhibition: Conditioning
579 stimulus intensity, recording site, and effects of 1 Hz repetitive TMS. *Brain*
580 *Stimul*. Elsevier Inc; 2011;4: 202–209. doi:10.1016/j.brs.2010.10.005
- 581 40. Ferreri F, Ponzo D, Hukkanen T, Mervaala E, Könönen M, Pasqualetti P,
582 et al. Human brain cortical correlates of short-latency afferent inhibition: a
583 combined EEG-TMS study. *J Neurophysiol*. 2012;108: 314–323.
584 doi:10.1152/jn.00796.2011
- 585 41. Hashimoto I, Gatayama T, Yoshikawa K, Sasaki M. Somatosensory

- 586 evoked potential correlates of psychophysical magnitude estimations for
- 587 air-puff stimulation of the face in man. *Exp Brain Res.* 1992;88: 639–644.
- 588 42. Nagamatsu K, Nakasato N, Hatanaka K, Kanno A, Iwasaki M, Yoshimoto
- 589 T. Neuromagnetic localization of N15, the initial cortical response to lip
- 590 stimulus. *Neuroreport.* 2001;12: 1–5. Available:
- 591 <http://www.ncbi.nlm.nih.gov/pubmed/11201065>
- 592 43. Nakahara H, Nakasato N, Kanno A, Murayama S, Hatanaka K, Itoh H, et
- 593 al. Somatosensory-evoked fields for gingiva, lip, and tongue. *J Dent Res.*
- 594 2004;83: 307–11. doi:10.1177/154405910408300407
- 595 44. Nevalainen P, Ramstad R, Isotalo E, Haapanen M-L, Lauronen L.
- 596 Trigeminal somatosensory evoked magnetic fields to tactile stimulation.
- 597 *Clin Neurophysiol.* 2006;117: 2007–2015.
- 598 doi:10.1016/j.clinph.2006.05.019
- 599 45. Nguyen BT, Inui K, Hoshiyama M, Nakata H, Kakigi R. Face
- 600 representation in the human secondary somatosensory cortex. *Clin*
- 601 *Neurophysiol.* 2005;116: 1247–1253. doi:10.1016/j.clinph.2005.01.018
- 602 46. Hoshiyama M, Kakigi R, Koyama S, Watanabe S, Shimojo M. Activity in
- 603 posterior parietal cortex following somatosensory stimulation in man:
- 604 Magnetoencephalographic study using spatio-temporal source analysis.
- 605 *Brain Topogr.* 1997;10: 23–30. doi:10.1023/A:1022206906360
- 606 47. Sakamoto K, Nakata H, Yumoto M, Kakigi R. Somatosensory processing
- 607 of the tongue in humans. *Front Physiol.* 2010;1 NOV: 1–10.
- 608 doi:10.3389/fphys.2010.00136
- 609 48. Forss N, Hari R, Salmelin R, Ahonen A, Hämäläinen M, Kajola M, et al.
- 610 Activation of the human posterior parietal cortex by median nerve

- 611 stimulation. *Exp Brain Res.* 1994;99: 309–315. doi:10.1007/BF00239597
- 612 49. Río-Rodríguez D, Iglesias-Soler E, Fernandez-del-Olmo M. Modulation of
613 quadriceps corticospinal excitability by femoral nerve stimulation.
614 *Neurosci Lett.* Elsevier Ireland Ltd; 2017;637: 148–153.
615 doi:10.1016/j.neulet.2016.11.033
- 616 50. Mancini F, Bauleo A, Cole J, Lui F, Porro CA, Haggard P, et al. Whole-
617 body mapping of spatial acuity for pain and touch. *Ann Neurol.* 2014;75:
618 917–924. doi:10.1002/ana.24179
- 619 51. Jacobs K, Donoghue J. Reshaping the cortical motor map by unmasking
620 latent intracortical connections. *Science* (80-). 1991;251: 944–947.
621 doi:10.1126/science.2000496
- 622 52. Bailey AZ, Mi YP, Nelson AJ. Short-latency afferent inhibition in chronic
623 spinal cord injury. *Transl Neurosci.* 2015;6: 235–243. doi:10.1515/tnsci-
624 2015-0025
- 625 53. Hahamy A, Macdonald SN, van den Heiligenberg F, Kieliba P, Emir U,
626 Malach R, et al. Representation of Multiple Body Parts in the Missing-
627 Hand Territory of Congenital One-Handers. *Curr Biol.* Elsevier Ltd.;
628 2017;27: 1350–1355. doi:10.1016/j.cub.2017.03.053
- 629 54. Makin TR, Bensmaia SJ. Stability of Sensory Topographies in Adult
630 Cortex. *Trends Cogn Sci.* Elsevier Ltd; 2017;21: 195–204.
631 doi:10.1016/j.tics.2017.01.002
- 632 55. Turco C V., El-Sayes J, Savoie MJ, Fassett HJ, Locke MB, Nelson AJ.
633 Short- and long-latency afferent inhibition; uses, mechanisms and
634 influencing factors. *Brain Stimul.* Elsevier Ltd; 2017; 1–16.
635 doi:10.1016/j.brs.2017.09.009

636 56. Di Lazzaro V, Pilato F, Dileone M, Profice P, Marra C, Ranieri F, et al. In
637 vivo functional evaluation of central cholinergic circuits in vascular
638 dementia. Clin Neurophysiol. International Federation of Clinical
639 Neurophysiology; 2008;119: 2494–2500. doi:10.1016/j.clinph.2008.08.010

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644 **Supporting information**

645 **S1 Appendix. Peak-to-peak mean MEP amplitudes (mV).** Excel file with
646 peak-to-peak mean MEP amplitudes (mV) values per condition per subject used
647 to perform the statistical analysis.

A.

Upper Lip

B.

Cheek

C.

Forearm

D.

Arm