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Face-hand sensorimotor interactions revealed by afferent inhibition

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-
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Abstract

Reorganization of the sensorimotor cortex following permanent (e.g., amputation) or temporary (e.g., local anaesthesia) deafferentation of the hand has revealed large-scale plastic changes between the hand and face representations that are accompanied by perceptual correlates. The physiological mechanisms underlying this reorganization remain poorly understood. The aim of this study was to investigate sensorimotor interactions between the face and hand using an afferent inhibition transcranial magnetic stimulation protocol in which the motor evoked potential elicited by the magnetic pulse is inhibited when it is preceded by an afferent stimulus. We hypothesized that if face and hand representations in the sensorimotor cortex are functionally coupled, then electrocutaneous stimulation of the face would inhibit hand muscle motor responses. In two separate experiments, we delivered an electrocutaneous stimulus to either the skin over the right upper lip (Experiment 1) or right cheek (Experiment 2) and recorded muscular activity from the right first dorsal interosseous. Both lip and cheek stimulation inhibited right first dorsal interosseous motor evoked potentials. To investigate the specificity of this effect, we conducted two additional experiments in which electrocutaneous stimulation was applied to either the right forearm (Experiment 3) or right upper arm (Experiment 4). Forearm and upper arm stimulation also significantly inhibited the right first dorsal interosseous motor evoked potentials, but this inhibition was less robust than the inhibition associated with face stimulation. These findings provide the first evidence for face-to-hand afferent inhibition.

Keywords: electrocutaneous stimulation; reorganization; sensorimotor integration; transcranial magnetic stimulation.

INTRODUCTION

The sensory and motor cortices contain somatotopic maps of body areas and muscles. The medio-lateral organization of these maps is such that the lower limb is represented medially followed by the trunk, arm, forearm and most laterally the hand and face with some degree of overlap between the different areas (Catani, 2017; Penfield & Boldrey, 1937; Sanchez Panchuelo et al., 2018).

The face and hand representations differ from those of other body parts because their proximity within the maps contrasts starkly with their separation in the physical body (Fang et al., 2002; Jain et al., 1997; Manger et al., 1997; Nakamura et al., 1998; Paullus & Hickmott, 2011; Penfield & Boldrey, 1937; Sanchez Panchuelo et al., 2018). Furthermore, the extensive area devoted to processing stimuli or controlling musculature from these two body parts is disproportionate to their physical size (Coq et al., 2004; Sur et al., 1980). Explanations for these curious aspects of sensorimotor organization include self-organization mechanisms, the position of the foetus in the womb and prenatal sensorimotor experience (Farah, 1998).

A morphologically distinct septum separates the face and hand areas both in the sensory (Jain et al., 1998) and motor (Kuehn et al., 2017) cortices. Despite this anatomical separation, there is some evidence that horizontal intracortical connections cross this border (Manger et al., 1997) and are capable of rapid excitatory and inhibitory synaptic plasticity (Paullus & Hickmott, 2011). This is consistent with the observation of both rapid and slow sensorimotor map reorganization involving the face area following a reduction of sensorimotor inputs from the hand. For example, many studies have found that amputation or temporary nerve block of the hand induce an enlargement and shift of the face's sensorimotor representation towards that of the hand (Flor et al., 1995; Pascual-Leone et al., 1996; Raffin et al., 2016; Ramachandran, 1993; Weiss et al., 2004). In the case of temporary block, these plastic changes can be seen in under 1 h, suggesting that they rely heavily on preexisting connections. This short-term plasticity is paralleled by behavioural changes like improved two-point discrimination on the upper lip after anaesthesia of hand nerves (median and radial nerves) (Weiss et al., 2004).

Permanent reduction of inputs from the hand sometimes, but not always (see, e.g., Makin et al., 2015), leads to the face representation taking over the whole hand area. This has been interpreted as evidence that this type of plasticity results from the reduction of inputs from the missing body part, but more recent studies suggest that it can also be due to increased inputs from other intact body parts: for example, when the lips or feet are used for hand functions (Hahamy et al., 2017; Makin et al., 2013; Striem-Amit et al., 2018). In line with this idea, we recently reported rapid plastic changes between the hand and face following an increase in somatosensory input on the hand (Muret et al., 2014, 2016). Three hours of repetitive somatosensory stimulation at the right index fingertip produced significant shifts in dipole location in the sensory cortex for both the index fingertip and the upper-lip and improved 2-point discrimination at the index fingertip and at the non-stimulated upper lip (Muret et al., 2014, 2016). This finger-to-lip transfer appears to be specific to the face, as a subsequent study showed that two-point discrimination was not improved on the forearm (Muret & Dinse, 2018).

Another example of face-hand interactions in healthy individuals comes from Tanosaki et al. (2003), who showed that somatosensory evoked magnetic fields induced by electrical stimulation of the thumb were altered when there was concurrent tactile stimulation of the upper face. This suggests that somato-sensory interactions exist between the face and the hand under conditions that do not involve plasticity. These findings raise the question of whether sensory-motor interactions between the face and the hand might also exist.

To investigate this question, we used the short-latency afferent inhibition (SAI) protocol to test for the existence of face-to-hand sensorimotor interactions. In this protocol, the amplitude of a muscle response (evoked by transcranial magnetic stimulation [TMS] of the motor cortex) is reduced when motor cortex stimulation is preceded by an afferent stimulus (Asmussen et al., 2013, 2014; Chen et al., 1999; di Lazzaro et al., 2002, 2005; Kukaswadia et al., 2005; Lapole & Tindel, 2015; Pilurzi et al., 2013; Sailer et al., 2002, 2003; Tamburin et al., 2001; Tokimura et al., 2000).

SAI protocols have already been widely used to examine sensori-motor interactions within the same body part. For example, hand muscle responses are strongly inhibited following stimulation of hand nerves or the skin on the fingertip (Asmussen et al., 2013, 2014; Bikmullina et al., 2009; Chen et al., 1999; di Lazzaro et al., 2002, 2005; Helmich et al., 2005; Kukaswadia et al., 2005; Lapole & Tindel, 2015; Pilurzi et al., 2013; Sailer et al., 2002, 2003; Tamburin et al., 2001; Tokimura et al., 2000), especially when the stimulus is given close to the target muscle (Dubbioso et al., 2017). Similarly, stimulation of the suprascapular nerve of the shoulder inhibits TMS-evoked responses in the shoulder muscle infraspinatus (Bradnam et al., 2016).

Afferent inhibition can also occur when the muscle of interest and the sensory stimulation site are in different segments of the same limb. For example, stimulation of the index fingertip inhibits various muscles of the upper arm and forearm on the

same side as the fingertip stimulation (Bikmullina et al., 2009), and stimulation of the dorsal surface of the foot inhibits responses in the leg muscle tibialis anterior (Ruddy et al., 2016).

To date, only two studies have investigated whether SAI exists between anatomically distant body parts that are not different segments of the same limb. The first examined interactions between the upper and lower limbs and found no evidence of SAI in lower limb muscles following afferent stimulation of the index finger, nor in upper limb muscles following afferent stimulation of the big toe (Bikmullina et al., 2009). The second examined interactions between distant body parts that constantly work together—the two hands. Unlike for the upper and lower limbs, they found that electrocutaneous stimulation on the hand inhibited hand muscles on the opposite side of the body (Ruddy et al., 2016).

Our interest in short-term plastic changes between the face and hand led us to wonder whether sensorimotor interactions involved in SAI exist between these two body parts. Thus, the aim of the present study was to further investigate SAI between anatomically distant body parts by examining whether SAI exists between two anatomically distant but cortically adjacent body parts, the face and the hand.

2 | MATERIALS AND METHODS

2.1 | Participants

Forty-four healthy right-handed volunteers were included in four separate experiments. It is important to note that each experiment was independent of the others, as the aim of this study was to investigate if and when electrocutaneous stimulation of the skin of a given body part could alter TMS-induced muscle responses in the right first dorsal interosseous (FDI). Fourteen individuals participated in Experiment 1 (mean age of 22.7 ± 7.1 years, five males), 12 in Experiment 2 (mean age of 23.7 ± 6.7 years, three males), 15 in Experiment 3 (mean age of 25.5 ± 6.4 years, two males) and 13 in Experiment 4 (mean age of 24.8 ± 3.9 years, three males).

These sample sizes were based on previous studies using SAI (Tokimura et al., 2000; Tamburin et al., 2001, 2005; di Lazzaro et al., 2002, 2005, 2007, 2008; Helmich et al., 2005; Bikmullina et al., 2009; Asmussen et al., 2013, 2014; Pilurzi et al., 2013; Ruddy et al., 2016; Bailey et al., 2016; Bradnam et al., 2016; Ríó-Rodríguez et al., 2017). Four subjects participated in two experiments (1 and 2 [$n = 2$]; 1 and 3 [$n = 1$]; 3 and 4 [$n = 1$]) and three subjects participated in three experiments (1–3 [$n = 1$]; 1, 3 and 4 [$n = 1$]; 2–4 [$n = 1$]).

All participants gave written informed consent. The protocol was approved by the ethical committees of the Grenoble University Hospital (ID RCB: 2016-A01668-43) and the Comité de protection des personnes SUD EST IV (ID RCB: 2010-A01180-39) and conformed to the ethical aspects of the Declaration of Helsinki.

2.2 | General experimental procedures

Participants were comfortably seated with their arm resting on an armrest (elbow flexed at 90), and a single tactile electrical stimulus was applied prior to a single transcranial magnetic stimulation pulse over the hand area of the left motor cortex. In all four experiments, the same motor cortex area was stimulated—the FDI hotspot in the left hemisphere—and motor evoked potential (MEP) amplitudes were recorded from the same muscle—the right FDI. The electrocutaneous stimulus was applied to the right upper lip (Experiment 1), right cheek (Experiment 2), right forearm (Experiment 3) or right upper arm (Experiment 4).

Some SAI protocols set the inter-stimulus interval (ISI) between the electrocutaneous stimulus and the TMS pulse individually for each subject by measuring the latency of the N20 component of their somatosensory evoked potential and then adding several milliseconds to adjust for the conduction time from primary somatosensory cortex (S1) to primary motor cortex (M1). Significant inhibition of the FDI has been reported at ISIs of N20 + 2 ms following afferent stimulation of the index fingertip (Bailey et al., 2016). Other SAI protocols use a range of predetermined ISIs (typically between 15 and 100 ms) (see Turco et al., 2018, for a review). Significant FDI inhibition has been reported using this approach at ISIs between 25 and 50 ms following stimulation of the skin on the ipsilateral (Bikmullina et al., 2009; Helmich et al., 2005; Tamburin et al., 2005) or contralateral upper limb (Ruddy et al., 2016). Since we wanted to investigate SAI between cortically close, but anatomically

distant body parts (some of which were within the same limb segment), we did not measure N20 latency but instead investigated a wide range of predetermined ISIs: 15, 25, 35, 45, 55, 65, 75 and 85 ms.

In all four experiments, 14 trials of each ISI plus 34 TMS-only trials were presented in a random order with an inter-trial interval between 5 and 8 s. Every 24 trials, the experiment was paused to give a short break to the participant. Experiments 1 and 2 were conducted in the IMPACT laboratory (Lyon, France) and Experiments 3 and 4 in the IRMaGe MRI and Neurophysiology facilities (Grenoble, France).

2.3 | Electrical stimulation

Electrocutaneous stimulation was achieved by delivering a brief, single pulse (square wave, 200 μ s) via a constant current stimulator (DS7A, Digitimer Ltd, UK) using adhesive electrodes (Neuroline 700, Ambu, Copenhagen, Denmark). The electrodes were placed on the face (upper-lip: exp 1 or cheek: exp 2) or the upper limb (forearm: exp 3 or upper arm: exp 4) in a bipolar configuration, and the electrocutaneous stimulation intensity was adjusted to be non-painful. The site of the electrocutaneous stimulation changed for each experiment, but motor cortex stimulation was always applied over the FDI hotspot in the left hemisphere.

The sensory perception threshold (SPT) for each electrocutaneous stimulation site was determined as the minimum stimulation intensity at which the subject reported feeling the stimulation on two out of three trials. The majority of SAI studies using cutaneous afferent stimulation use a stimulation intensity of 3xSPT. It is important to note, however, that SAI increases with increasing afferent stimulation but decreases in the presence of pain (see Turco et al., 2018, for a review). To maximize our chances of observing sensory afferent inhibition, we initially stimulated all body parts at 3xSPT, but after some pilot testing, we reduced the stimulation intensity on the cheek and upper lip to 2xSPT since 3xSPT was painful for most participants. Thus, perceived stimulation intensity was matched across all four stimulation sites. The absolute electrocutaneous stimulus intensities used in each experiment are shown in Table 1, and the Kruskal-Wallis test by ranks revealed no differences between each of the four experiments ($H_3 = 5.342$; $p = 0.15$).

2.3.1 | Experiment 1: SAI between the right upper lip and the right FDI

Two electrodes were placed over the right upper lip, separated by 1 cm. One electrode was close to the philtral ridge, and the other was positioned laterally, just above the oral commissure. The electrodes were positioned along the horizontal line running between the middle of the philtrum and the zygomatic process of the maxilla (the inferior tip of the cheek bone)—in the territory of the infraorbital nerve (Figure 1a). Stimulation was delivered at 2xSPT.

TABLE 1 Average electrocutaneous and TMS stimulus intensities used in each of the four experiments, plus average TMS-only amplitude of FDI MEPs (mean SEM)

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

Note: In all four experiments, TMS was applied over the hand area of the motor cortex, and MEPs were recorded from FDI.

Abbreviations: ES, electrocutaneous stimulation; MSO, maximum stimulator output; rMT, resting motor threshold; TMS-only, FDI MEP amplitude in the absence of electrocutaneous stimulation.

2.3.2 | Experiment 2: SAI between the right cheek and the right FDI

Two electrodes were placed over the right cheek, separated by 1 cm. One electrode was positioned at the midpoint of the line running between the right tragus and the right oral commissure, and the other was positioned above it, over the zygomatic bone—in the territory of the zygomaticofacial nerves (Figure 1a). Stimulation was delivered at 2xSPT.

2.3.3 | 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—in the territory of the musculocutaneous nerve (Figure 1b). Stimulation was delivered at 3xSPT.

2.3.4 | Experiment 4: SAI between the right upper arm and the right FDI

Electrodes were placed 1.5 cm apart on the medial face of the upper arm in the middle of the proximal third of the upper arm on the skin overlying the border between the biceps and the triceps—in the territory of the intercostobrachial nerve (Figure 1b). Stimulation was delivered at 3xSPT.

2.4 | Transcranial magnetic stimulation and electromyography

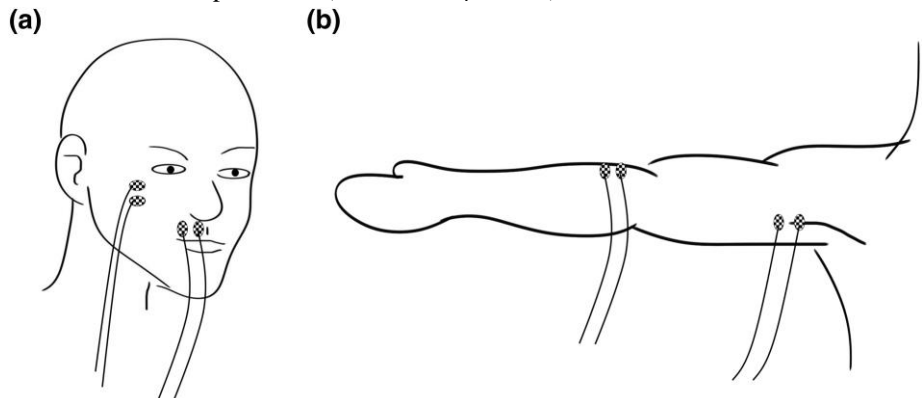
In all four experiments, TMS was applied over the left motor cortex, and EMG activity was recorded from the right FDI via surface electrodes (DE-2.1, Delsys, Massachusetts, USA) placed on the muscle belly. EMG activity was recorded at 2,000 Hz, digitized (Power 1401II, Cambridge Electronics Design, Cambridge, 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 100 stimulator (Magventure, Skovlunde, Denmark).

The scalp vertex (CZ) and the C3 cranial references were marked on the participant's scalp to facilitate location of the left M1 hand area which is close to C3. The coil was positioned over C3 with the handle pointing backwards approximately 45 to the sagittal plane. The optimal point for stimulating FDI was found by stimulating various sites around C3 at a slightly suprathreshold intensity and identifying the site with the largest, most stable responses. A single TMS pulse maximally stimulates a small area under the coil as well as surrounding brain areas (Wagner et al., 2009), but systematic assessment of the spatial sensitivity of TMS has revealed it to be as low as 4 mm (Harquel et al., 2017), and it can be used to selectively stimulate two hand muscles in the same hand (Raffin et al., 2015).

To enable the experimenter to accurately maintain the coil over the optimal position throughout the experiment, the optimal stimulation point was recorded in a neuro-navigation system (Brainsight, Rogue Resolutions, Cardiff, UK [Experiments 1 and 2], Localite neuronavigation system, Localite GmbH, Sankt Augustin, Germany [Experiments 3 and 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 1 mV. The average rMT and intensity that produced a MEP of approximately 1 mV (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 ($H_3 = 2,598$; $p = 0.46$).

FIGURE 1 Face and upper limb skin regions stimulated in each experiment. Drawing representing the electrode positions for delivering electrocutaneous stimulation in the skin over the face (a) and upper limb (b) for each experiment



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

2.5 | Statistical analysis

Peak-to-peak MEP amplitudes (mV) were measured offline using custom-written Spike 2 or Signal scripts (Cambridge Electronics Design, Cambridge, UK). Trials were excluded if they were contaminated by muscle contraction or if their amplitudes were greater than or less than 1.96 SDs from the mean of that condition for that subject. For Experiment 1, an average of 16 (8.8 SD) out of 146 trials were excluded; 19 (6.3 SD) out of 146 trials (Exp 2); 13 (6.2 SD) out of 147 trials (Exp 3) and 18 (8.8 SD) out of 150 trials (Exp 4). The small variation in the total number of trials per experiment (146–150) was due to the delivery of extra TMS-only pulses in Experiments 3 and 4. The number of trials excluded did not differ across the four experiments (one-way analysis of variance: $F_{3, 50} = 1.670$; $p = 0.1852$).

Given the variability and heteroscedasticity of the raw MEP amplitudes, the statistical analyses were carried out using generalized linear mixed-effect models. Each model included data from all four experiments, and for each subject, MEP amplitudes from each trial were normalized to the mean of the TMS-only condition for that subject. We analysed the influence of two possible fixed effects: (i) Body-Part (four levels: Upper Lip, Cheek, Forearm, Upper Arm); and (ii) ISI (numerical values between 0 [no afferent stimulus] and 85). To fit the ISI effect, since we did not know whether the mean structure was generated as a polynomial, we chose a more flexible structure; a cubic spline with 7 degrees of freedom. We accounted for inter-subject variability by defining subjects as effects with random intercepts. We accounted for betweenbody-part variability in the ISI factor by defining them as effects with random slope, thus instructing the model to correct for any systematic differences between these variabilities. We accounted for testing site variability (Exp. 1 and 2: IMPACT laboratory; Exp. 3 and 4: IRMaGe MRI and Neurophysiology facilities) by adding a factor to inform the model of this possible source of variance. The Lmer of R lme4 package provides tools to analyse mixed effects of linear models (Bates et al., 2015). We used Wald chi-squared tests (Fox & Weisberg, 2011) to perform type II analysis of variance. For post hoc tests, the emmeans package in R (Lenth et al., 2019) was used, and p values were considered as significant at $p < 0.05$ and Bonferonni-adjusted for the number of comparisons. Since our statistical approach assumes heterogeneity rather than homogeneity of variance, instead of calculating the power, it is generally preferred to use the R-squared—an estimation of goodness of fit—to estimate the quality of the model.

Statistical analyses were performed using Prism 5, v. 5.02 (GraphPad, San Diego, CA, USA) and the statistical programming language R.4.1.0 (R Core Team, 2016, Vienna, Austria). Raw data (peak-to-peak MEP amplitudes [mV]) for all four experiments are included in Appendices S1–S4.

3 | RESULTS

In order to investigate if electrocutaneous stimulation on the face (upper-lip: exp 1 or cheek: exp 2) or the upper limb (forearm: exp 3 or upper arm: exp 4) inhibited MEPs in the right FDI, we performed a generalized linear mixed-effect model analysis that included data from all trials and all four experiments. Our model presented a high goodness-of-fit with an R squared of 0.72, while still controlling for over-fitting by taking into account Akaike information criterion (AIC) and Bayesian information criterion (BIC) estimations.

This analysis revealed that MEP amplitudes in the right FDI were reduced when the TMS pulse was preceded by an electrocutaneous stimulus on the upper lip, cheek, forearm or upper arm, but the pattern of inhibition differed for the four stimulation sites as it was present at different ISIs for each of body part and was more robust for stimulation applied to the upper lip and cheek. Figure 2 shows examples of MEPs from two representative subjects who each participated in two experiments (one in the upper lip and cheek experiments and one in the upper arm and forearm experiments). To facilitate clarity, MEPs are plotted for the TMS only condition and the 15, 55 and 85 ms ISIs. Visual inspection of this figure reveals consistent inhibition of FDI MEPs at the 55 ms ISI compared to the TMS-only condition in all four examples.

The Wald Chi-Squared test on the generalized linear mixed model revealed significant main effects of body part ($\chi^2_3 = 10.681$, $p = 0.014$) and ISI ($\chi^2_6 = 128.600$, $p < 0.001$) and a significant interaction between body part and ISI ($\chi^2_{18} = 54.165$, p

< 0.001). For each body part, we performed a series of Bonferroni-corrected post hoc tests comparing the MEP amplitude at each ISI against the TMS-only MEP amplitude ($\Delta_{\text{TMS-only/ISI}}$). These tests revealed significant inhibition between the upper lip and FDI at three consecutive ISIs: 45 ms

($\Delta_{\text{TMS-only/ISI}} = 0.27826$, $\text{SE}_{\text{TMS-only/ISI}} = 0.0567$, $p < 0.0001$), 55 ms ($\Delta_{\text{TMS-only/ISI}} = 0.37779$, $\text{SE}_{\text{TMS-only/ISI}} = 0.0523$, $p < 0.0001$) and 65 ms ($\Delta_{\text{TMS-only/ISI}} = 0.32067$, $\text{SE}_{\text{TMS-only/ISI}} = 0.0560$, $p < 0.0001$) (Figure 3a). Inhibition between the cheek and FDI was significant at four consecutive ISIs: 35 ms ($\Delta_{\text{TMS-only/ISI}} = 0.22044$, $\text{SE}_{\text{TMS-only/ISI}} = 0.0627$, $p = 0.0035$), 45 ms ($\Delta_{\text{TMS-only/ISI}} = 0.35846$, $\text{SE}_{\text{TMS-only/ISI}} = 0.0589$, $p < 0.0001$), 55 ms ($\Delta_{\text{TMS-only/ISI}} = 0.38899$, $\text{SE}_{\text{TMS-only/ISI}} = 0.0571$, $p < 0.0001$) and 65 ms ($\Delta_{\text{TMS-only/ISI}} = 0.29102$, $\text{SE}_{\text{TMS-only/ISI}} = 0.0649$, $p = 0.0001$) (Figure 3b).

The pattern of inhibition between forearm and upper arm and FDI differed from that of the upper lip and cheek, as forearm stimulation produced significant inhibition at three non-consecutive ISIs: 25 ms ($\Delta_{\text{TMS-only/ISI}} = 0.16526$, $\text{SE}_{\text{TMS-only/ISI}} = 0.0542$, $p = 0.0184$), 65 ms ($\Delta_{\text{TMS-only/ISI}} = 0.16329$, $\text{SE}_{\text{TMS-only/ISI}} = 0.0571$, $p = 0.0341$) and 85 ms ($\Delta_{\text{TMS-only/ISI}} = 0.18695$, $\text{SE}_{\text{TMS-only/ISI}} = 0.0627$, $p = 0.0230$) (Figure 3c) and upper arm stimulation produced significant inhibition at only one ISI: 55 ms ($\Delta_{\text{TMS-only/ISI}} = 0.16839$, $\text{SE}_{\text{TMS-only/ISI}} = 0.0572$, $p = 0.0259$) (Figure 3d).

4 | DISCUSSION

4.1 | Face-hand SAI

Here, we present the first evidence of sensorimotor afferent inhibitory interactions between the face and the hand. Both cheek and lip stimulation inhibited hand MEPs by approximately 25% at ISIs between 35 and 65 ms.

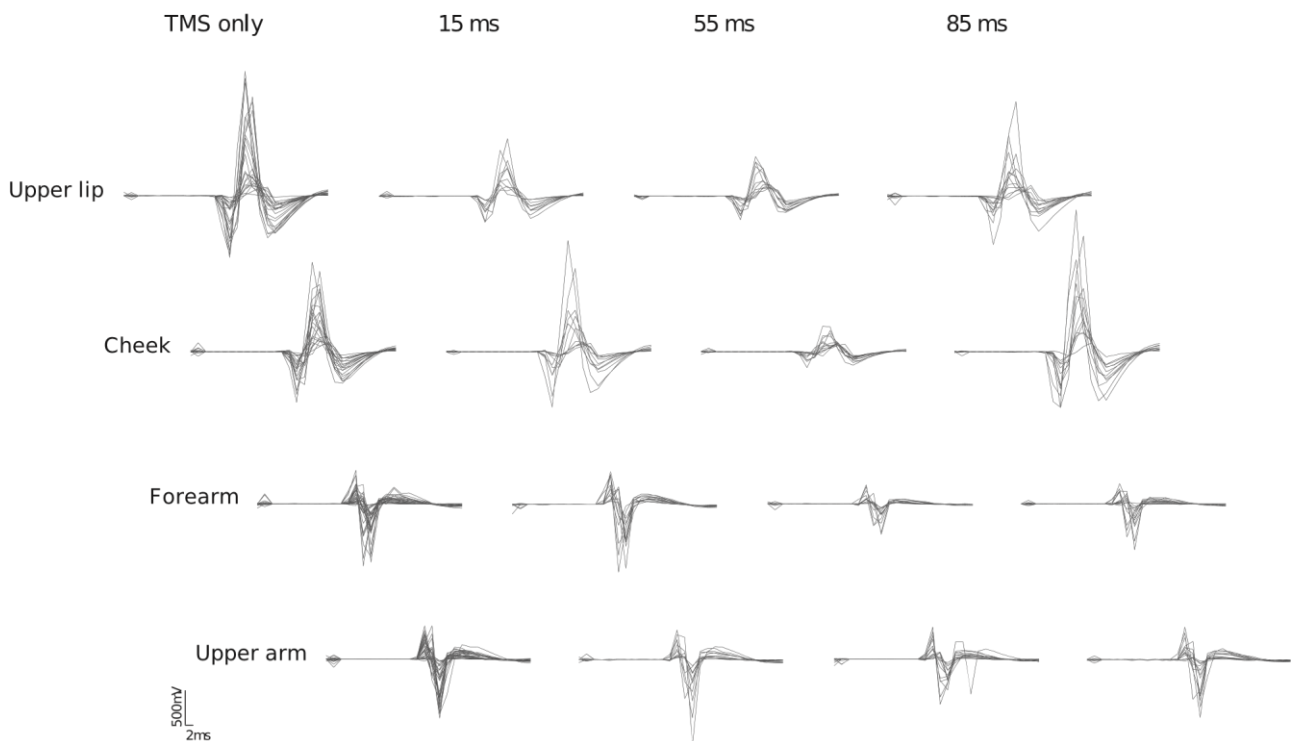


FIGURE 2 Example of MEPs from individual subjects from all four experiments for the TMS-only, 15, 55 and 85 ms ISIs. The figure shows all valid MEPs from two representative subjects: one who participated in the face experiments (upper lip and cheek electrocutaneous stimulation) and the other who participated in the upper limb experiments (forearm and arm electrocutaneous stimulation)

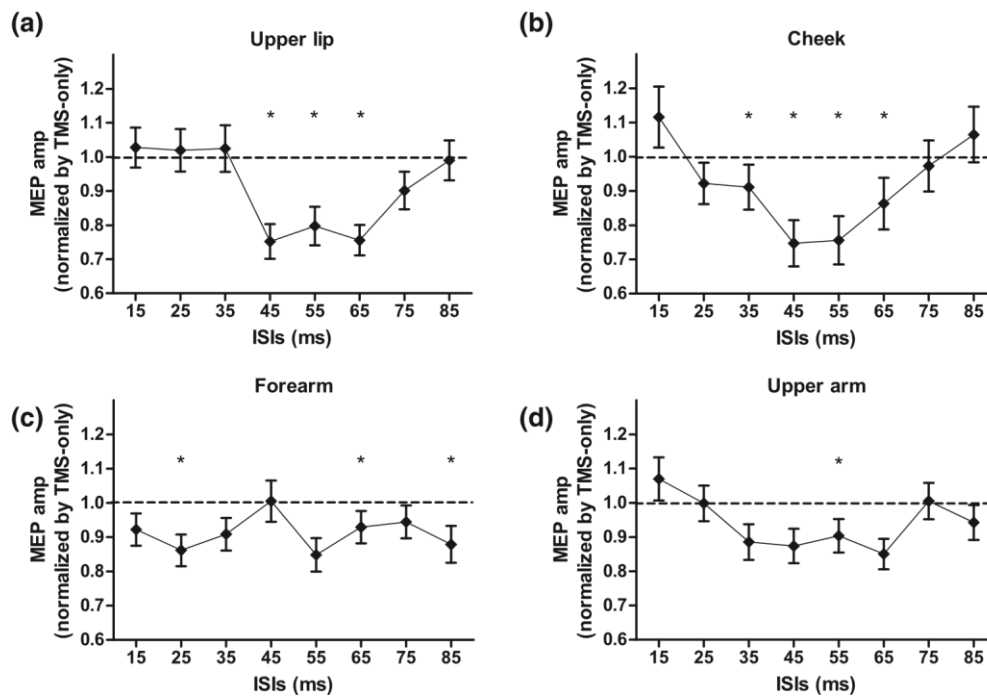


FIGURE 3 Normalized mean MEP amplitudes in the right FDI after electrocutaneous stimulation of (a) the right upper lip—Experiment 1; (b) the right cheek—Experiment 2; (c) the right forearm—Experiment 3; and (d) the right upper arm—Experiment 4. Bars represent the standard error of the mean (SEM). The black dashed lines represent the TMS-only MEP amplitude. Asterisks represent significant Bonferroni-corrected post hoc tests ($p < 0.05$) comparing TMS-only MEP amplitude with MEP amplitude at each ISI

In studies of hand-hand SAI, inhibition typically begins at ISIs around 25 ms. This is the approximate time necessary for the afferent volley to arrive in S1 and to be transferred to the motor cortex, which has led to the hypothesis that SAI results from the activation of interneurons that inhibit M1 corticospinal pyramidal cells (di Lazzaro et al., 2007; Turco et al., 2018).

There are only two published studies of face-face SAI (Pilurzi et al., 2013, 2020), and only one reported significant inhibition. Pilurzi et al. (2020) found significant inhibition in a face muscle following stimulation of the trigeminal nerve as early as 15 ms—a delay consistent with the direct activation of S1 to M1 connections like that observed in hand-hand SAI. Interestingly, while stimulation of the trigeminal nerve inhibited MEPs at short intervals facial nerve stimulation did not, and the reverse was true for ISIs longer than 100 ms (Pilurzi et al., 2020).

If face-hand afferent inhibition were based upon the same pathways as hand-hand and face-face SAI, we would have expected to observe SAI between the face and hand at our shortest ISI (15 ms). Instead, inhibition was present between 35 and 65 ms. This is consistent with data from Pilurzi et al. (2020) showing inhibition (not statistically significant) between the face and the hand at 30 ms (their fig. 8A). It is also consistent with results of the only other published study to examine facehand inhibition at ISIs longer than 30 ms which found that stimulation of a facial nerve significantly inhibited FDI MEPs at ISIs between 30 and 60 ms, but not at shorter ISIs (Siebner et al., 1999). Face-hand afferent inhibition thus appears to involve different, longer pathways from those involved in hand-hand or face-face SAI.

Electroencephalography and magnetoencephalography studies have shown that when a somatosensory stimulus arrives in S1, it evokes a series of positive (P) and negative (N) deflections between 15 ms (N15) and 65 ms (P65) (Hashimoto et al., 1992; Nagamatsu et al., 2001; Nakahara et al., 2004; Nevalainen et al., 2006; Nguyen et al., 2005). Other deflections are also measurable at longer latencies (70–120 ms), and these are thought to reflect later stages of somatosensory processing within the secondary somatosensory cortices (Hoshiyama et al., 1997; Nguyen et al., 2005; Sakamoto et al., 2010). Our finding of significant face-hand inhibition at ISIs between 35 and 65 ms suggests that the inhibition we observed does not involve activation in secondary somatosensory cortices. Thus, face-hand SAI may rely on early somatosensory processing, albeit via less direct pathways than face-face or hand-hand SAI.

4.2 | Upper-arm-hand SAI

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 (Asmussen et al., 2013, 2014; Bikhullina et al., 2009; Chen et al., 1999; Helmich et al., 2005; Sailer et al., 2002, 2003; Tamburin et al., 2001; Tokimura et al., 2000), shoulder-shoulder (Bradnam et al., 2016), leg-leg (Río-Rodríguez et al., 2017) or between different limb segments (hand!arm muscle, hand!forearm muscle, Bikhullina et al., 2009;

Helmich et al., 2005; Tamburin et al., 2005; foot/leg muscle, Ruddy et al., 2016). On the basis of these studies, afferent inhibition within the upper limb appears to be a robust phenomenon. It may thus be surprising that we did not observe robust SAI in the FDI when we stimulated the forearm and upper arm. It is important to note, however, that only one other study of afferent inhibition within the upper limb applied a protocol similar to ours in which the afferent stimulation was applied to areas other than the hand (Bikmullina et al., 2009). In this study, above-elbow stimulation of the posterior cutaneous brachial nerve at 3xSPT at ISIs of 18 and 28 ms did not inhibit hand (or other arm) muscles. In contrast, we observed SAI following upper arm stimulation, but MEP amplitudes began to decrease at 35 ms, and inhibition was only significant at 55 ms.

Similar to the face-hand inhibition discussed above, this occurred at ISIs consistent with the activation of non-monosynaptically connected populations in S1 and M1. In contrast to the face, however, inhibition was smaller (15% vs. 25%), and occurred at fewer and nonconsecutive ISIs.

The inhibitory interactions between the face and hand revealed here might constitute one of the mechanisms underlying face-hand cortical reorganization (Farnè et al., 2002; Raffin et al., 2016; Weiss et al., 2004). As suggested by Jacobs and Donoghue (1991), one possible mechanism of cortical reorganization is the unmasking of pre-existing lateral intracortical excitatory connections via the reduction of activity in intracortical inhibitory circuits. The inhibitory sensorimotor interactions observed here might contribute to maintaining functional boundaries between face and hand cortical territories and might be one of the potential physiological substrates upon which a multitude of remotely represented body parts may enter a (missing) hand territory based upon the frequency of usage of these body parts (Hahamy et al., 2017; Makin et al., 2013; Makin & Bensmaia, 2017).

One possible limitation of this study was the inclusion of more female subjects in all experiments. While there are currently no data on gender-related differences in SAI, intracortical inhibition is higher in females (Shibuya et al., 2016) and is affected by menstrual cycle phase (Smith et al., 1999).

5 | CONCLUSION

In spite of increasing interest in afferent inhibition, its underlying function remains unknown (reviewed in Turco et al., 2018). Some studies use it as a tool to investigate the integrity of the cholinergic system (di Lazzaro et al., 2002, 2008), while others use it as we did here: as a tool to probe sensorimotor interactions in neurologically healthy individuals (Asmussen et al., 2014; Chen et al., 1999; Lapole & Tindel, 2015; Pilurzi et al., 2013; Tamburin et al., 2001). The experiments presented in this paper constitute an important step in investigating the existence of SAI between body parts and provide the first evidence for the presence of SAI between the face and the hand.

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CONFLICT OF INTEREST

The authors declare that they have no competing interests.

AUTHOR CONTRIBUTIONS

BR, JM, AF and KR did study concept and design. BR, JM, ER, SH and KR collected data. BR, JM, ER, SH, RB, AF and KR did data analysis and interpretation. BR, JM and KR did the drafting of the manuscript. BR, JM, ER, SH, RB, AF and KR did the critical revision of the manuscript.

PEER REVIEW

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DATA AVAILABILITY STATEMENT

All relevant data are fully available within the manuscript and in its supporting information files.

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