



Stimulating the deprived motor ‘hand’ area causes facial muscle responses in one-handers



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Introduction

How the brain adapts to the absence of sensory inputs and motor outputs from early development is a key question in neuroscience. While sensory deprivation has long been known to trigger changes to cortical maps in sensory and motor cortex, e.g. due to blindness [1], deafness [2] or arm malformation [3], there is an ongoing debate on their functional relevance. For example, using fMRI, we have previously reported that the deprived sensorimotor hand territory of individuals born without a hand shows increased activity evoked by movements of the lips, feet and residual arm, when compared to two-handed controls [4,5]. This is consistent with the idea that the missing-hand area may be recruited to support increased representation of alternative intact body parts. However, changes to cortical map boundaries (i.e., remapping), as measured through fMRI, do not necessarily entail changed representational content and readout [3]. As such, the observed remapping may not subservise a functional role. By allowing to directly stimulate the motor cortex and measure the evoked muscular responses in various body parts, TMS provides a unique opportunity to causally assess the functional consequences of motor remapping.

Few previous studies have used this technique to investigate the functional content of the missing-hand area of individuals with congenital limb deficiencies. In people born without both hands and with exceptional foot dexterity, TMS over the missing-hand area elicited MEPs in the feet and interfered with foot movements [6,7]. In congenital one-handers, studies have focused on the residual arm [8–10], with mixed evidence: two studies reported an expansion of the residual arm representation [8,9], but this has not been replicated [10]. Here, we used single-pulse TMS to investigate the functional relevance of the previously observed remapping of the lips in the missing-hand motor cortex of one-handers [4,5]. We hypothesised that functional reorganisation should result in facial MEPs when the missing-hand area is activated.

Methods

To this end, we stimulated the missing-hand region in 10 congenital one-handers (OH) and the non-dominant hand area in 10 two-handed controls (CT), and measured EMG activity from the muscle surrounding the mouth (orbicularis oris). The missing-hand region was defined by first locating the motor hotspot of the intact first dorsal interosseous muscle and then flipping the coordinates onto the other hemisphere using a neuronavigation software (BrainSight, Rogue Research). The stimulation intensity was set to 150% of the resting motor threshold (rMT) of the intact-hand hotspot. We administered 30 pulses with muscles at rest and 15 pulses during slight lip contraction (for details, see ‘Supplementary Methods’; or <https://osf.io/6n7s8/> to full study protocol and EMG data).

Peak-to-peak amplitudes and MEP response latencies were examined for all trials showing an MEP. The proportion of individuals showing face MEPs across groups was compared using Fisher’s Exact Test. Whenever possible, we also stimulated the face hotspot ipsilateral to the missing hand with an intensity of 120% rMT and compared the face MEP latencies of the two stimulation locations (missing-hand vs. face hotspot) with Welch’s t-tests. When non-significant differences were found, we calculated the Bayes factor (Cauchy prior width = 0.707) to obtain the likelihood of observing our data under the null hypothesis.

During stimulation, we additionally recorded EMG from a prominent residual arm muscle in one-handers, or the non-dominant forearm extensor in controls. The arm recordings were used to confirm that we were stimulating close to the (missing) hand region. We compared the MEP arm latency of ‘face-responders’ (participants that showed face MEPs during missing-hand stimulation) to controls using two-tailed Bayesian tests for single case assessment [11]; see Fig. S1 for group comparisons. One one-hander (OH4) had a transhumeral arrest, making the comparison to controls’ forearm muscles inadequate. As a substitute, an image of the participant’s MRI scan overlaid with the stimulation coordinates was used to confirm the stimulation location (Fig. S2).

Results

We observed clear arm MEPs in 6 out of 10 one-handers and in all controls. Of these 6 one-handers, 3 showed face MEPs during lip contraction trials (Fig. 1) while, importantly, no face MEPs were found in controls (Fig. S3). Average MEP amplitude and latencies were as follows: OH2 (87% MEP-trials): 0.47 mV ($SD = 0.13$ mV) and 11.5 ms ($SD = 0.4$ ms); OH4 (93% MEP-trials): 0.29 mV

($SD = 0.07$ mV) and 12.5 ms ($SD = 1.0$ ms); OH5 (93% MEP-trials): 0.36 mV ($SD = 0.10$ mV) and 12.2 ms ($SD = 0.9$ ms). The remaining one-handers showed either a strong decay artefact in the facial EMG or did not show face MEPs (Fig. S3). A Fisher's Exact Test confirmed that face MEPs are more common in one-handers than controls ($p = 0.036$). During rest trials, no clear face MEPs were observed (Fig. S4).

Additionally, we stimulated the face hotspot in two of the three face-responders. Average MEP amplitudes and latencies were as follows: OH4 (100% MEP-trials): 0.57 mV ($SD = 0.13$ mV) and 11.2 ms ($SD = 1.5$ ms); OH5 (74% MEP-trials): 0.20 mV ($SD = 0.07$ mV) and 12.5 ms ($SD = 0.3$ ms). In OH4, face MEPs from the face hotspot had shorter latencies compared to the face MEPs from the missing-hand hotspot ($W(24.61) = 2.9, p < 0.01$). OH5 showed no significant differences in latencies across the two stimulation locations ($W(15.68) = -1.17, p = 0.26, BF(01) = 1.7$). Importantly, in

both cases the shape of the MEPs looks similar for the two stimulation locations (Fig. S5) suggesting that the observed facial EMG-signal during missing-hand stimulation are indeed MEPs. No arm MEPs were observed during face-hotspot stimulation.

All face-responders (OH2, OH4, OH5) exhibited arm MEPs during missing-hand stimulation (Fig. 1). The Bayesian test for single case assessment revealed no differences in arm MEP latencies between OH5 ($M = 17.6$ ms, $SD = 0.5$ ms) and controls ($Z = 0.41, p = 0.7$), with an estimated 65% of the control population falling below OH5's value, and between OH2 ($M = 14.8$ ms, $SD = 1.4$ ms) and controls ($Z = -1.97, p = 0.09$), with an estimated 2.5% of the control population falling below OH2's value. These findings provide indirect evidence that it is unlikely that we stimulated closer to the face region in the face-responders compared to controls ($M = 17.1$ ms, $SE = 0.4$ ms; Fig. S1), for OH4 see Fig. S2.

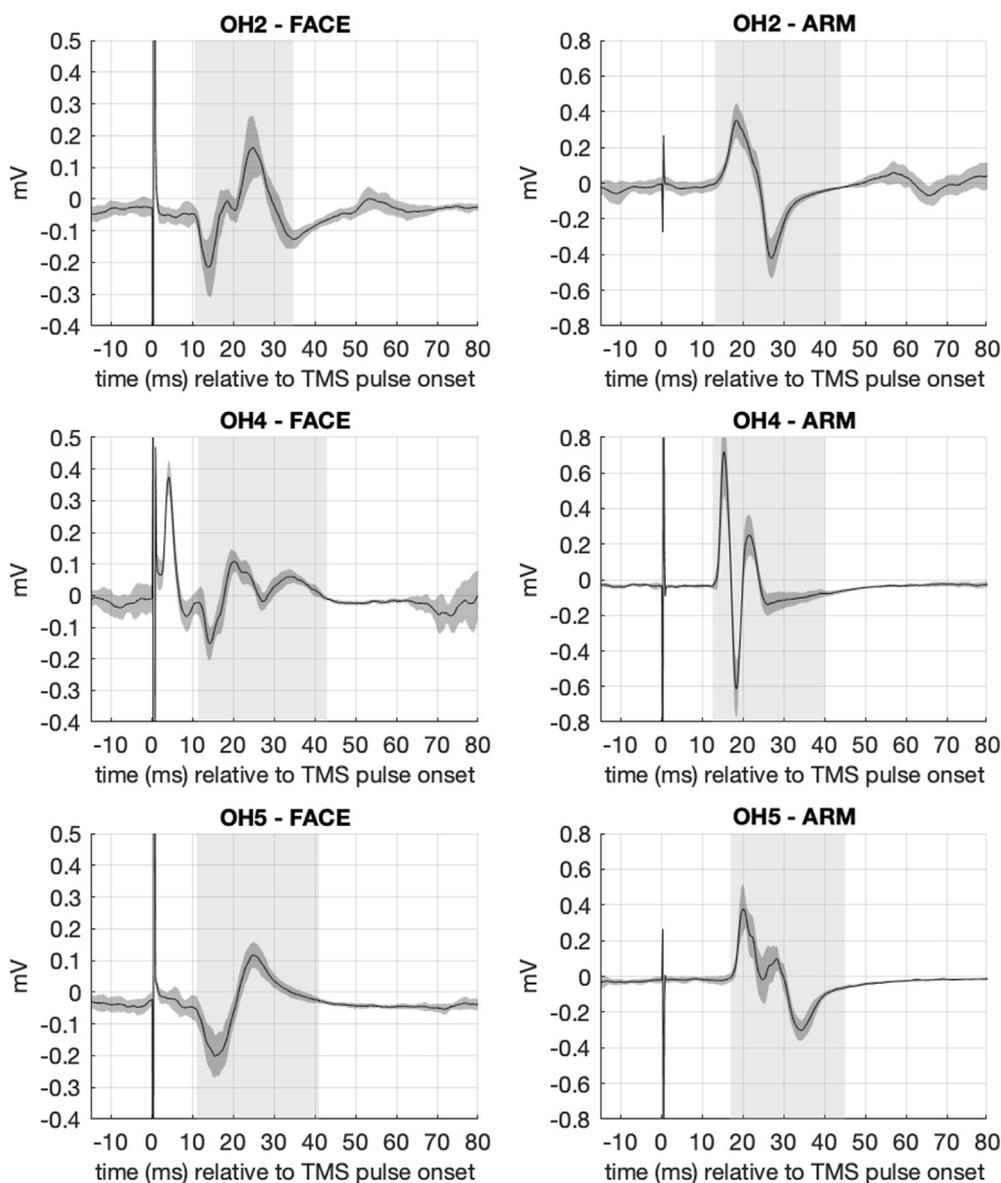


Fig. 1. Average EMG from the orbicularis oris (left) and residual arm muscle of face-responders for all lip contraction trials during missing-hand stimulation (solid line: mean value; shaded area: \pm one standard deviation). The mean MEP-window is highlighted in light grey. For OH4, the spike at around 5 ms reflects a peripherally evoked compound muscle action potential (CMAP).

Discussion

Here, we show that muscle responses in the lower face can be evoked in a subgroup of congenital one-handers by applying single-pulse TMS over the missing-hand motor area. The normative values and shape of these observed MEPs are in line with previous research directly stimulating the face area [12]. The fact that MEP latencies evoked from the missing-hand and face sites are not conclusively similar in our sample, with OH4 reporting increased latencies from the missing-hand site, suggests that a mono-synaptic corticospinal projection from the missing-hand area is likely unsuited to explain our findings [13]. Rather, although our data contain no direct evidence, it appears more plausible that the observed MEPs are generated through cortico-cortical projections through horizontal connections from the missing-hand to the face site [14].

By showing that the missing-hand motor area can engage in motor control of the lower face muscles, we provide direct evidence for functionally relevant sensorimotor reorganisation in congenital one-handers. We suggest that, in absence of the typical peripheral input/output sensorimotor dynamics during development, the sensorimotor missing-hand area becomes responsive to face inputs, otherwise normally inhibited. This hypothesis is supported by the findings of increased global connectivity and decreased GABA in the missing-hand area, indicating decreased inhibition in one-handers [4]. Our present results suggest that such release from inhibition has functional consequences.

Interestingly, we only detected facial motor responses in a subset of one-handed participants. This could be due to methodological reasons (see Supplementary Methods), but it could also indicate that the patterns of functional reorganisation differ across one-handed individuals. It was suggested that patterns of remapping in the deprived hand area may be dictated by the relative compensatory use of alternative body parts during development, due to mechanisms of Hebbian-like plasticity [4]. Under this framework, only individuals who have used their mouth more frequently to compensate for the missing-hand functions would show functional reorganisation of the face. However, since one-handers predominantly rely on their residual arm for compensatory behaviours, this framework would have predicted shorter arm MEP latencies, which was not consistently observed here (Fig. S1). Nevertheless, our unique dataset provides a rare opportunity to demonstrate that deprivation-triggered plasticity, which results in new functional outcomes, is possible in the human brain even in absence of exceptional training [as in 6,7]. Further research using longitudinal approaches is needed to better understand the role of motor experience in shaping brain reorganisation as it unfolds across development.

Declaration of competing interest

The authors confirm that there are no known conflicts of interest associated with this publication and there has been no financial support for this work that could have influenced its outcome.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.brs.2021.01.022>.

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