BRIEF COMMUNICATION

Altered cortical activation from the hand after facial botulinum toxin treatment

Sara Haenzi[1], Gabor Stefanics[2,3], Tatjana Lanaras[4], Maurizio Calcagni[4] & Arko Ghosh[1,5]

[1]Institute of Neuroinformatics, University of Zurich and ETH Zurich, Switzerland
[2]Translational Neuromodeling Unit, University of Zurich and ETH Zurich, Switzerland
[3]Laboratory for Social and Neural Systems Research, University of Zurich, Switzerland
[4]Division of Plastic and Reconstructive Surgery, University Hospital Zurich, Switzerland
[5]Neuroscience Center Zurich, University of Zurich and ETH Zurich, Switzerland

Correspondence

Arko Ghosh, Institute of Neuroinformatics, University of Zurich and ETH Zurich, Winterthurerstr. 190, Zurich CH-8057, Switzerland. Fax: +41 44 635 3053; E-mail: arko@ini.uzh.ch

Abstract

Plastic interactions between face and hand cortical tactile circuits occur after severe injuries that affect the hand such as in amputation or spinal cord injury. However, whether loss of facial movements alters the cortical circuits involved in processing tactile inputs from the hand remains unknown. In this prospective observational study we used electroencephalography (EEG) to measure cortical activity evoked by tactile stimulation of the hands before and after botulinum toxin-A-induced facial paralysis. We found a reduction in the tactile event-related potentials (ERPs) 6 weeks after the treatment. This suggests that the limited paralysis of facial muscles induced during cosmetic interventions designed to smooth lines and wrinkles on the face is sufficient to alter the cortical processing of tactile inputs from the hand.

Introduction

Cervical spinal cord injury or hand amputation can induce intriguing plastic interactions between the hand and the face cortical circuits. In nonhuman primates, after a dorsal column lesion in the cervical spinal cord the somatosensory cortical territory responsive to tactile inputs from the face widens and shifts into the territory deprived of sensory inputs from the hand.[1,2] Similarly, in humans and nonhuman primates amputation of the hand widens and shifts the face cortical territory.[3,4] Remarkably, the physiological changes after the amputation can be accompanied by phantom sensation of the hand when the face is touched.[5] The proximity between face and hand territories in the somatosensory cortex may underlie these interactions.[2,5] Nevertheless, whether cortical activity evoked by tactile stimulation from the hand alters after a facial dysfunction has not been systematically addressed.

There are a few clinical observations indicating that the cortical activity associated with the hand is altered in facial dysfunction. First, in one patient with a surgical lesion of the trigeminal ganglion, phantom face sensations could be evoked by touching the hand.[6] Second, patients with painful trigeminal neuralgia on the right show higher amplitude event-related potentials (ERPs) in response to electrical stimulation of the right hand than in controls, but none of the patients experienced referred facial sensations from the hand.[7] Third, patients with facial palsy show enhanced hand-associated metabolic activity in the somatosensory cortex.[8] Finally, motor representations of the hand are altered in patients with hemifacial spasms after botulinum toxin-A (BT-A)-induced facial paralysis.[9]

In this observational study, we focused on people with no neurological conditions who underwent facial paralysis with BT-A to treat self-perceived lines and wrinkles. The paralysis induced by BT-A lasts for approximately 2 months.[10] As cosmetic BT-A injections are preplanned we were able to measure cortical activity in response to tactile stimulation of the hand *before* and *after* the paralysis, making the analyses highly sensitive to any changes.

Volunteers and Methods

Volunteers

Healthy outpatients predetermined to receive cosmetic BT-A injections to treat self-perceived forehead wrinkles were approached using mass emails. Twenty volunteers agreed to participate in the study and they received BT-A injections (median age 32 years, range 25–44 years, 15 women, 19 right-handed). Another 20 volunteers were drawn from the general public to form the control group such that each volunteer in the experimental group had a corresponding partner in the control group with the same age, gender, and handedness. Two volunteers from each group were subsequently eliminated due to technical reasons (see below). None of the volunteers had previously received cosmetic BT-A injections or were under prescription drugs. Written informed consent was obtained from all of the volunteers, and the Canton of Zurich's ethical committee approved all of the procedures.

BT-A injections

Each volunteer in the experimental group received a total of 14 injections containing BT-A (VISTABEL®, Allergan, Inc., Irvine, CA, total dose 12–44 units) to create a bilateral gradient with high BT-A concentrations at the glabella that decreased along the lateral axis along the forehead. This pattern of injections is routinely used in cosmetic clinics to paralyze the corrugator and frontalis muscles to treat frown lines and forehead wrinkles, respectively. The forehead paralysis was verified using electromyography electrodes on the frontalis muscle and video-based assessments of facial expressions.

Electroencephalography recordings

Pretest measurements were conducted 1–3 weeks before the BT-A injections and posttest measurements were conducted 5–6 weeks after the injections. The volunteers in the control group were also measured twice, with a gap of 6–9 weeks between the measurements.

Brief suprathreshold tactile pulses were applied on either thumb in a random order. Stimuli consisted of a single 2 msec long tap delivered using a solenoid tapper (Heijo Electronics, Beckenham, UK), which made a 12.5 mm^2 contact with the thumb pulp and resulted in 0.4 mm indentation on the pulp. The stimulus was presented 1250 times on either thumb and the interstimulus interval was 1500 ± 250 msec. The taps were silent, still a background audible white noise was played to ensure that the taps remained inaudible through the experiment. Similarly, the forehead was also stimulated but this data

is not presented here due to the high incidence of facial muscle artifacts.

Continuous electroencephalography (EEG) was recorded from 62 Ag-AgCl electrodes mounted to an equidistant elastic cap (EasyCap, Inning am Ammersee, Germany). The signals were amplified with an AC coupled amplifier that had hardware imposed high-pass of 0.016 Hz (BrainAmp MR, Brain Products GmbH, Gilching, Germany). The data were re-referenced offline to the average signals from all of the scalp electrodes.

The data were further analyzed with EEGLAB, an open source Matlab toolbox. The data were band-pass filtered between 0.5 and 30 Hz, and trials affected by blink or other artifacts were rejected from further analysis by applying a ±50 μV threshold to all channels. A median of 750 artifact free trials (out of 1250 stimulations) was extracted from either thumb per volunteer per session. Two volunteers were excluded from each group due to excessive blinking or sweating.

The data from the left and right hand stimulations were statistically analyzed separately using the Matlab toolbox LIMO-EEG.[11] Pre- and posttest repeated measures mixed-design analyses of variance were conducted using the general linear model framework and were corrected for multiple comparisons using two-dimensional spatio-temporal clustering based on 1000 bootstraps (significance threshold $P = 0.05$).[11] The BT-A treatment effect was reflected in the group × time interaction (F-statistic).

Results

We instructed all the volunteers to perform forehead movements and in the experimental group BT-A injections visibly paralyzed the muscles bilaterally (involuntary movements of the forehead were not tested). Visual inspection of the tactile ERPs identified positive peaks at ~50, 100, and 200 msec after tactile stimulus onset near the contralateral somatosensory cortices (at electrodes C3 and C4, according to the international 10–20 system), corresponding to the canonical P50, P100, and P200.[12,13]

We analyzed the data across all electrodes and time points. Forehead paralysis significantly reduced the amplitude of the contralateral P200 wave evoked by the left thumb stimulations (Fig. 1A–C). Topographic maps of repeated measures statistics (F-statistics) revealed that the alterations were restricted to the electrodes above the contralateral somatosensory cortex (Fig. 1D). Forehead paralysis also reduced the responses to right thumb stimulation (Fig. 1E–H). ERPs to right thumb stimulations were significantly reduced in both hemispheres, although most significant reductions were found at left hemispheric sites above the somatosensory cortex (Fig. 1H).
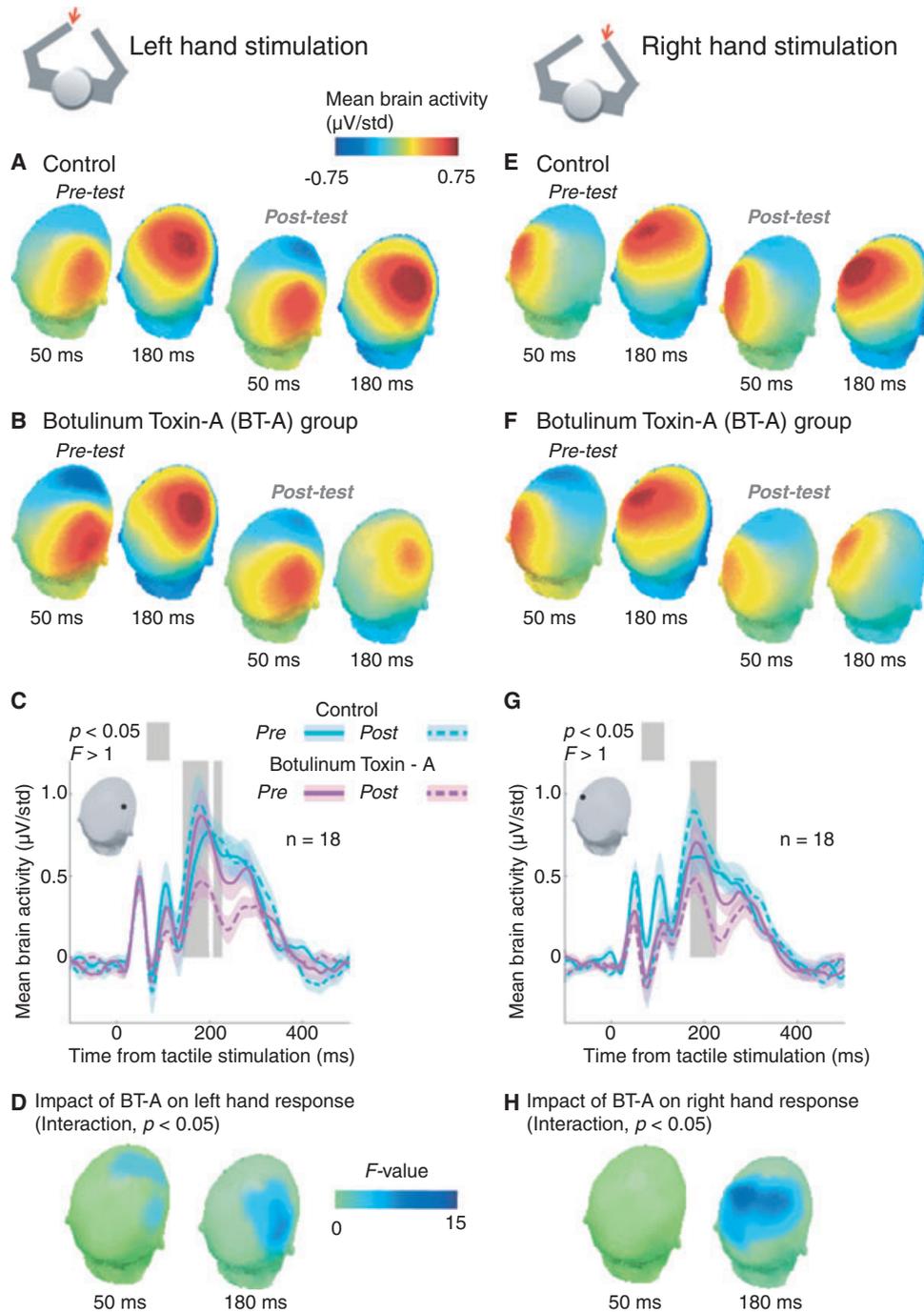
Figure 1. Botulinum toxin-A (BT-A) injections in the forehead decreased cortical tactile event-related potentials (ERPs) evoked from the hands. Tactile stimuli were applied to the left (A–D) or the right (E–H) thumbs. (A) Three-dimensional (3D) topographic maps of brain activity in the control group were calculated by using the average of linearly modeled ERPs. The times below each plot indicate the time point after stimulation. (B) 3D topographic maps of brain activity in the experimental group show a reduction in cortical activity after the BT-A injection. (C) Averaged traces recorded from the electrode with the highest mean activity. The gray inset shows the electrode location on a 3D scalp representation. Solid lines indicate the mean brain activity values at each time point, and the shaded lines represent standard errors. The time points shaded with gray showed significant effects of BT-A. (D) 3D topographic maps of the statistical measure (F-statistic) demonstrate the spatial distribution of the effects of BT-A injections on left hand-evoked cortical responses. (E) 3D topographic maps of brain activity in the control group calculated using the average of linearly modeled ERPs. (F) 3D topographic maps of brain activity in the BT-A injected group show a reduction in cortical activity. (G) Averaged traces recorded from the electrode with the highest mean activity. (H) 3D topographic maps of the statistical measure (F-statistic) demonstrate the spatial distribution of the effects of BT-A injections on right hand-evoked cortical responses. The effects of BT-A on right hand-evoked responses were observed in both hemispheres, but were more prominent in the left hemisphere.

Discussion

Previous physiological studies on hand amputees revealed enlargement of the face representation in the somatosensory cortex.[3,5,14] Furthermore, clinical observations on patients with facial sensory or motor abnormalities indicated that their hand representation is enlarged.[6–9] Taken together, they suggest that the face–hand plastic interactions result in a widening of the cortical representation of one body part in response to injury affecting the other body part. Here we studied cortical ERPs evoked by tactile stimulation of the hand in first time cosmetic BT-A users. We found reduced P200 wave evoked from either hand after 6 weeks of BT-A injections on the forehead. This study indicates that a period of limited facial paralysis alters the cortical processing of sensory inputs from the hand. We expected an increase in the amplitude of the ERPs from the hand after the facial paralysis and yet this was not found, indicating that the cortical response to a limited facial paralysis is intrinsically different from the response to substantial loss of function such as in amputation or facial nerve injury.

It is unlikely that our findings were due to the direct impact of BT-A. The toxin is restricted to the injection site and its immediate surroundings. BT-A induces paralysis by interrupting the motor outputs of the nerve terminals that innervate the muscles. Presumably, the toxin does not directly affect the sensors on the skin that are sensitive to touch and movements. However, because forehead movements generate sensations by moving the skin and stretching spindle-like sensors, limited paralysis deprives the brain of the sensory inputs that are generated by forehead movements, thus indirectly affecting the sensory pathways. This deprivation may have provided the impetus for the changes observed here.

The high temporal resolution of the ERPs provided some insights into the stages of tactile processing from the hands affected by the facial paralysis. As the paralysis did not change the early P50 and P100 waves, a marked reorganization in the initial stages of tactile processing from the thalamus to the primary somatosensory cortex was unlikely.[15] We observed a significant reduction in the later P200 wave. This wave presumably reflects neuronal activity in the secondary somatosensory area.[15] It is indeed possible for plastic changes to occur in the secondary area independent of the primary area due to the parallel processing of sensory inputs in the somatosensory cortex.[16]

In light of previous work on face–hand neuronal plasticity it was unclear why the ERPs from the hand reduced after the facial paralysis. However, this study differed from the previous reports in three important ways. First, unlike the severe injuries affecting the hand or face stud-

ied previously the main impact of BT-A was restricted to just a few muscles. Second, the previous reports on face–hand interactions mainly focused on lower parts of the face, but BT-A injections were restricted to the forehead. Nevertheless, there is some evidence that forehead stimulation can result in phantom hand sensations in amputees.[14,17] Unlike the lower parts such as the lips, the forehead occupies only a small territory close to the thumb in the somatosensory cortex.[18–20] Finally, both sensory inputs and motor outputs are interrupted after a severe injury such as in limb amputation or spinal cord injury, but in this study tactile inputs were presumably left entirely intact from the forehead. As a consequence, the impotent forehead motor commands generated by the brain were followed by an unusual sensory feedback and these inconsistent inputs might have altered cortical sensory processing through NMDA-mediated synaptic plasticity.[21] Overall, the forehead paralysis induced by BT-A may have triggered a distinct set of mechanisms than in the severe injuries studied previously.

Previous reports on the modulation of the somatosensory P200 wave may provide some mechanistic insight into its reduction after BT-A. The amplitude of the P200 wave is modulated by attention, anesthetics, and analgesics, and appears altered in diseases affecting the cerebral cortex.[22] Importantly, patients with temporo-parietal junction lesions show reduced P200 amplitude.[23] This cortical area is thought to integrate sensory inputs from different modalities. In addition, the P200 amplitude is enhanced for congruent visuo-tactile events.[24] We speculate that the inputs from the face and hand are integrated such that reduction in sensory inputs due to BT-A-induced facial paralysis diminishes the P200 evoked from the hand. This would predict that a minor dysfunction of the hand would diminish the P200 obtained from the face. The speculated form of face–hand interaction must be overcome in larger injuries such as in hand amputation or facial nerve lesions by parallel processes such as unmasking of preexisting connections and the compensatory use of the intact body part.[25]

To conclude, both the face- and the hand-associated cortical tactile circuits can respond to functional loss of the non-corresponding body part. Although it is established that the face representation in the cortex can widen after traumatic loss of the hand, our results indicate that hand loses cortical activity after a relatively small loss of facial movements. Using somatosensory ERPs alone we could not address whether the size of the hand territory is diminished by facial BT-A treatment. Another limitation was that we did not address whether the cortical changes were limited to the hands or whether they could be generalized to other body parts. Further research is needed to unravel the etiology, time-course, extent, and

behavioral consequences of the cortical alterations induced by a limited facial paralysis.

Acknowledgments

Conflicts of Interest

Drs. Lanaras and Calcagni routinely perform clinical procedures that involve products made by Allergan. Ms. Haenzi, and Drs. Stefanics and Ghosh have no interests to declare.

References

1. Tandon S, Kambi N, Lazar L, et al. Large-scale expansion of the face representation in somatosensory areas of the lateral sulcus after spinal cord injuries in monkeys. J Neurosci 2009;29:12009–12019.

2. Pons TP, Garraghty PE, Ommaya AK, et al. Massive cortical reorganization after sensory deafferentation in adult macaques. Science 1991;252:1857–1860.

3. Grusser SM, Muhlnickel W, Schaefer M, et al. Remote activation of referred phantom sensation and cortical reorganization in human upper extremity amputees. Exp Brain Res 2004;154:97–102.

4. Florence SL, Kaas JH. Large-scale reorganization at multiple levels of the somatosensory pathway follows therapeutic amputation of the hand in monkeys. J Neurosci 1995;15:8083–8095.

5. Ramachandran VS, Rogers-Ramachandran D, Stewart M. Perceptual correlates of massive cortical reorganization. Science 1992;258:1159–1160.

6. Clarke S, Regli L, Janzer RC, et al. Phantom face: conscious correlate of neural reorganization after removal of primary sensory neurones. NeuroReport 1996;7:2853–2857.

7. Tinazzi M, Valeriani M, Moretto G, et al. Plastic interactions between hand and face cortical representations in patients with trigeminal neuralgia: a somatosensory-evoked potentials study. Neuroscience 2004;127:769–776.

8. Rijntjes M, Tegenthoff M, Liepert J, et al. Cortical reorganization in patients with facial palsy. Ann Neurol 1997;41:621–630.

9. Liepert J, Oreja-Guevara C, Cohen LG, et al. Plasticity of cortical hand muscle representation in patients with hemifacial spasm. Neurosci Lett 1999;272:33–36.

10. Blitzer A, Brin MF, Keen MS, Aviv JE. Botulinum toxin for the treatment of hyperfunctional lines of the face. Arch Otolaryngol Head Neck Surg 1993;119:1018–1022.

11. Pernet CR, Chauveau N, Gaspar C, Rousselet GA. LIMO EEG: a toolbox for hierarchical LInear MOdeling of ElectroEncephaloGraphic data. Comput Intell Neurosci 2011;2011:831409.

12. Montoya P, Sitges C. Affective modulation of somatosensory-evoked potentials elicited by tactile stimulation. Brain Res 2006;1068:205–212.

13. Hamalainen H, Kekoni J, Sams M, et al. Human somatosensory evoked potentials to mechanical pulses and vibration: contributions of SI and SII somatosensory cortices to P50 and P100 components. Electroencephalogr Clin Neurophysiol 1990;75:13–21.

14. Hunter JP, Katz J, Davis KD. The effect of tactile and visual sensory inputs on phantom limb awareness. Brain 2003;126:579–589.

15. Allison T, McCarthy G, Wood CC, et al. Human cortical potentials evoked by stimulation of the median nerve. II. Cytoarchitectonic areas generating long-latency activity. J Neurophysiol 1989;62:711–722.

16. Liang M, Mouraux A, Iannetti GD. Parallel processing of nociceptive and non-nociceptive somatosensory information in the human primary and secondary somatosensory cortices: evidence from dynamic causal modeling of functional magnetic resonance imaging data. J Neurosci 2011;31:8976–8985.

17. Knecht S, Henningsen H, Elbert T, et al. Reorganizational and perceptional changes after amputation. Brain 1996; 119(Pt 4):1213–1219.

18. Servos P, Engel SA, Gati J, Menon R. fMRI evidence for an inverted face representation in human somatosensory cortex. NeuroReport 1999;10:1393–1395.

19. Moulton EA, Pendse G, Morris S, et al. Segmentally arranged somatotopy within the face representation of human primary somatosensory cortex. Hum Brain Mapp 2009;30:757–765.

20. Nguyen BT, Tran TD, Hoshiyama M, et al. Face representation in the human primary somatosensory cortex. Neurosci Res 2004;50:227–232.

21. Friston K. A theory of cortical responses Philos Trans R Soc Lond B Biol Sci 2005;360:815–836.

22. Colon EJ, de Weerd AW. Long-latency somatosensory evoked potentials. J Clin Neurophysiol 1986;3:279–296.

23. Yamaguchi S, Knight RT. Anterior and posterior association cortex contributions to the somatosensory P300. J Neurosci 1991;11:2039–2054.

24. Longo MR, Musil JJ, Haggard P. Visuo-tactile integration in personal space. J Cogn Neurosci 2012;24:543–552.

25. Buonomano DV, Merzenich MM. Cortical plasticity: from synapses to maps. Annu Rev Neurosci 1998;21:149–186.