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Letter to the Editor

Botulinum Toxin-A dose dependent perceptual loss on the hand after its cosmetic use on the face

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Face-hand interactions are a hallmark of neuronal plasticity, such as in amputation or spinal cord injury. After a period of functional loss of the hand the cortical face representation is reorganized (Ramachandran, Rogers-Ramachandran, & Stewart, 1992). Similarly, a period of functional loss of the face can reorganize the hand representation (Rijntjes et al., 1997). These intriguing mutual interactions may be due to the close proximity of face and hand representations in the somatosensory and motor cortices (Kaas, 1991).

Botulinum Toxin-A (BT-A) is widely used to treat facial wrinkles and a single treatment acts to paralyze muscles for around 2 months (Garcia & Fulton, 1996). We recently found by using EEG that the hand associated cortical activity is altered in healthy people after a period of limited facial paralysis induced by BT-A (Haenzi, Stefanics, Lanaras, Calcagni, & Ghosh, 2014). Here we evaluated the perceptual performance by using tactile temporal order judgment (TOJ) on the hands *before* and *after* the cosmetic treatment. This task involves both somatosensory and pre-motor cortical representations to integrate spatial and temporal signals (Takahashi, Kansaku, Wada, Shibuya, & Kitazawa, 2013). Previous studies show that the performance in this task declines with aging and is poorer in patients with abnormal motor control (Craig, Rhodes, Busey, Kewley-Port, & Humes, 2010; Fiorio, Tinazzi, Bertolasi, & Aglioti, 2003). Surprisingly, in our study we found dose-dependent decline in the performance within six weeks of BT-A injections.

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1. Methods

Twenty-nine volunteers agreed to receive BT-A injections and participate in this study (median age 33 year, 24 females). In 40 volunteers, i.e., 20 BT-A treated and 20 untreated controls, we measured tactile temporal order judgments on the thumbs. In the remaining 9 BT-A treated volunteers we focused our measurements on the toes. The volunteers in control group were from the general public (age-sex-handedness matched to BT-A group). None of the volunteers had previously received BT-A or were under prescription drugs during the study. BT-A (VISTABEL®, Allergan, Inc., USA) was injected bilaterally around the glabella. The injection dose (reported here in total Allergan's units injected in the volunteer's forehead) was determined by the surgeon partly based on each volunteer's esthetic taste for the extent of paralysis, pre-existing wrinkles and a qualitative assessment of the muscle strength. The perceptual measurements were acquired before and after the treatment. To elaborate, tactile temporal order judgments from the left and right thumbs or toes were recorded .5–3 weeks before and 5–6 weeks after the injections. Volunteers in the control group were recorded with a gap of 6–9 weeks (therefore, the same inter-measurement interval was maintained for the two groups). Each measurement session consisted of several consecutive inter-limb tactile stimulations and volunteers reported the limb on which the touch was felt first – 'left' or 'right'. Tactile stimuli were presented with computer controlled solenoid tappers (Heijo Electronics, UK). Each stimulation lasted for 2 ms. The inter-stimulation intervals (also referred to as stimulus onset asynchronies or SOAs) were ±5, ±15, ±25, ±35, ±45, ±55, ±75, and ±95 ms. The volunteers were subjected to 16 trials for each SOA. For each SOA we quantified the response probability as the number of right-first responses divided by 16. The probabilities were then used towards individual psychometric function fitting (Palamedes toolbox). The slopes of the psychometric functions that related the SOAs and the probability of right-first responses were used to calculate the Just Noticeable Differences (JND; JND = .675/slope; ±.675 represents the 25% and 75% points on the cumulative normal distribution). Essentially, JND measured the time gap needed to correctly respond to 75% of the trials. Statistical analyses of the data were conducted using ANCOVA (IBM SPSS Statistics, USA) and linear regressions (MATLAB, USA). The ethical committee in Zurich approved the experiments and written informed consent was obtained from each volunteer.

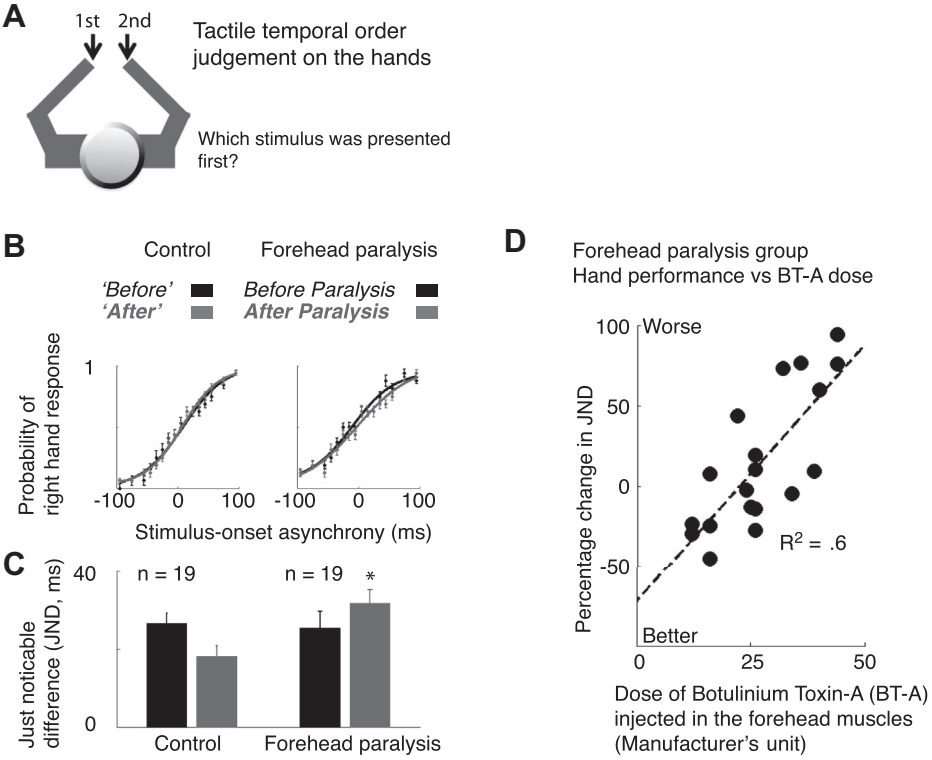

Fig. 1 – The hands displayed altered tactile acuity after forehead paralysis. (A) Tactile stimuli were applied to the thumbs with a pair of solenoid tappers that generated 2 ms long gentle stimulations at varying interstimuli intervals. The volunteers then reported the temporal order of the presented stimuli. (B) Psychometric functions were fitted to the group medians. The error bars indicate the standard errors for each time point. (C) The just noticeable difference (JND) measurements demonstrated a subtle but significant increase after 6 weeks of forehead paralysis. ANCOVA was used for statistical analysis. * indicates $p < .05$. The bars and error bars represent the group median JNDs and standard errors. Larger JND values indicate poorer tactile acuity. (D) There was a correlation between BT-A dose and JND value. JND values increased with higher doses of the toxin.

2. Results and discussion

We evaluated tactile perception by stimulating both thumbs with a pair of solenoid tappers (Fig. 1A). One volunteer was eliminated from each group due to the inability to sit through the experiment. Psychometric functions were used to assess the relationship between the SOA and the probability of picking one of the thumbs (median $R^2 = .9 \pm .2$ SEM). We used these psychometric functions to determine the JND, and larger JND values were associated with poorer perceptual accuracy. After adjusting for pre-test measures, we found that forehead paralysis reduced the tactile acuity of the thumbs (Fig. 1C; $F_{1,37} = 4.69$; $p < .05$; and partial $\eta^2 = .12$). The smallest dose that was used resulted in visible muscle paralysis. However, the latency until onset of paralysis and the number of paralyzed motor fibers are determined by the dose (Garcia & Fulton, 1996). Remarkably, the percentage change in JND between the pre- and post-test measurements positively correlated with the injected dose (Fig. 1D; $R^2 = .6$; $F_{1,17} = 24.37$; and $p < .001$). Thus, higher doses of BT-A resulted in poorer tactile acuity on the thumbs. However, no such loss was detected on the toes ($R^2 = .01$; $F_{1,7} = .04$; and $p =$ n.s/0.85). Taken together, these results suggested that targeted forehead paralysis diminished the perceptual accuracy of the hands.

The perceptual changes documented may reflect maladaptive changes in the cortical hand representation akin to the reorganization that occurs leading to the phantom sensations in limb amputees (Ramachandran et al., 1992). However, we cannot entirely rule out that our results are due to the direct action of BT-A on the brain. In a previous study using rats with much higher doses of BT-A, the toxin was transported from the injection site into the brain (Antonucci, Rossi, Gianfranceschi, Rossetto, & Caleo, 2008). In our study we used much lower doses and therefore, maladaptive cortical plasticity was more likely to occur than the direct impact of BT-A on the brain. Furthermore, if BT-A directly acted on the brain it would presumably affect the foot in a dose-dependent manner, and yet this was not found. Prospective studies could provide a more accurate etiology. We suspect that the perceptual changes are more severe in repeated users of BT-A where the paralysis is sustained for much longer periods.

Author contributions

Dr. Ghosh had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Financial disclosure

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Drs. Lanaras and Calcagni routinely perform clinical procedures using products manufactured by Allergan (the manufacturer of Botulinum Toxin-A used in this study), and have participated in meetings at which Allergan was a sponsor. These authors have no further disclosures.

Other contributions

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Conflict of interest

Drs. Lanaras and Calcagni routinely perform clinical procedures that involve products made by Allergan and they have attended meetings sponsored by Allergan.

REFERENCES

Antonucci, F., Rossi, C., Gianfranceschi, L., Rossetto, O., & Caleo, M. (2008). Long-distance retrograde effects of botulinum neurotoxin A. *The Journal of Neuroscience, 28*, 3689–3696.

Craig, J. C., Rhodes, R. P., Busey, T. A., Kewley-Port, D., & Humes, L. E. (2010). Aging and tactile temporal order. *Attention, Perception, & Psychophysics, 72*, 226–235.

Fiorio, M., Tinazzi, M., Bertolasi, L., & Aglioti, S. M. (2003). Temporal processing of visuotactile and tactile stimuli in writer's cramp. *Annals of Neurology, 53*, 630–635.

Garcia, A., & Fulton, J. E., Jr. (1996). Cosmetic denervation of the muscles of facial expression with botulinum toxin. A dose-response study. *Dermatologic Surgery, 22*, 39–43.

Haenzi, S., Stefanics, G., Lanaras, T., Calcagni, M., & Ghosh, A. (2014). Altered cortical activation from the hand after facial botulinum toxin treatment. *Annals of Clinical and Translational Neurology, 1*, 64–68.

Kaas, J. H. (1991). Plasticity of sensory and motor maps in adult mammals. *Annual Review of Neuroscience, 14*, 137–167.

Ramachandran, V. S., Rogers-Ramachandran, D., & Stewart, M. (1992). Perceptual correlates of massive cortical reorganization. *Science, 258*, 1159–1160.

Rijntjes, M., Tegenthoff, M., Liepert, J., Leonhardt, G., Kotterba, S., Muller, S., et al. (1997). Cortical reorganization in patients with facial palsy. *Annals of Neurology, 41*, 621–630.

Takahashi, T., Kansaku, K., Wada, M., Shibuya, S., & Kitazawa, S. (2013). Neural correlates of tactile temporal-order judgment in humans: an fmri study. *Cerebral Cortex, 23*, 1952–1964.