Plastic changes in the brain after human hand allotransplantation

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Vascularized composite allotransplantation of the hand is technically feasible and is the only option to recover a lost hand after amputation. However, universal acceptance of this surgical reconstruction as a medical standard of care has not been achieved for the uncertainty of outcome after surgery.¹ We performed an exploratory study to examine the neurophysiologic changes in the somatosensory and primary motor cortices after hand transplant.

Methods

Standard protocol approvals, registrations, and patient consents

The protocol was approved by the University Health Network Research Ethics Board. The patient is a 49-year old woman who suffered a traumatic left (non-dominant) forearm and hand amputation 10 years before the study. She provided written informed consent and received hand allotransplantation. Restoration of sensory and motor functions began at 1–4 months and substantial functional recovery was reached 6–12 months after surgery (table S1, doi.org/10.5061/dryad.prr4xgxb).

A longitudinal study was designed to evaluate the cortical plastic changes 4 months before and up to 6 months after the surgery. Somatosensory mapping was performed using functional magnetic resonance imaging with electrical cutaneous stimulation (10 Hz, 4 seconds, 10 blocks) over upper arm and thumb. Transcranial magnetic stimulation mapping was performed to evaluate the changes in motor cortical representation. We tested intracortical circuits with a paired-pulse paradigm.

Results

Somatosensory mapping showed that representation for upper arm on the transplant side was located anterior-laterally compared to the intact side before surgery and moved posterior-medially at 6 months after surgery while that for the intact side was stable over time (figures 1, A and S1, doi.org/10.5061/dryad.prr4xgxb). The resting motor threshold and “1 mV” stimulus intensity for the biceps were higher than those for abductor pollicis brevis muscle in the intact arm while the measurements for biceps muscle on the transplant side were similar to those for the intact abductor pollicis brevis muscle before surgery and gradually increased after surgery (table S2). The magnetic stimulation mapping revealed that the motor cortical representation on the intact side did not change over time. For the biceps muscle on the transplant side, it was at a more anterior-lateral location before surgery and moved gradually in the posterior-medial direction after surgery (figures 1, B and S2). Interhemispheric inhibition from the symmetric position of motor hotspot for intact muscle on the transplant side (mirrored point) to the intact side and short-interval intracortical inhibition on the transplant side were absent before surgery and increased gradually after surgery (figure 1, C). The inhibition on the intact side (figures S3 and S4) and intracortical facilitation on either side did not change. Supplementary dataset is available from Dryad: doi.org/10.5061/dryad.prr4xgxb.

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Discussion

Hand allotransplantation is currently limited to highly selected patients for the complexity and uncertainty surrounding the surgery.^{1,2} The somatotopy of sensorimotor cortex comprises a medial to lateral topography for the leg, trunk and arm.^{2,3} Mature brain is still plastic, providing a basis for the flexibility and capability of functional reorganization with the

environment changes.³ Previous studies reported that the transplanted hand and face were eventually controlled in a normal fashion with significant plasticity of the adult brain and overlapping representations of different body parts in the sensorimotor cortex.^{2,4-6} However, it is not clear how the cortical representation of the transplanted hand is reintegrated and the cortical plasticity is correlated to the changes in cortical circuits after surgery. We demonstrated that cortical

Figure 1 Cortical representations and cortical circuits

(A) Somatosensory representation with cutaneous stimulation was tested 4 months before (red) and 6 months (green) after the hand transplant surgery. The effects of cutaneous stimulation on the right thumb (intact side) and left upper arm (transplant side) were tested in different sessions. The sensory representations obtained from different sessions (pre-vs post-surgery; different stimulation sites) were overlaid on a single-subject template using the Montreal Neurological Institute coordinates. The left image shows overview of the cortical areas with volume rendering of all 2D slides. All the activated sites were labeled with 3D coordinates. The stimulation of the thumb on the intact side activated similar cortical sites before and after transplant surgery. The site of activation produced by stimulation of upper arm on the transplant side was close to a mirror location for the intact thumb before hand transplant and shifted to a more posterior-medial position after surgery. The top right images are 3 axial images with different Z coordinates showing sites of activation for different experimental conditions: the site activated by stimulation of the thumb on the intact side (left, both before and after surgery), the sites activated by stimulation of the upper arm on the transplant side before surgery (middle) and 6 months after surgery (right). The bottom right image shows sites of activation for all experimental conditions in a coronal view. Color points (red and green) refer to sites of activation by cutaneous stimulation with $p < 0.05$ (t test with Bonferroni's correction). (B) TMS mapping (4 months before and 1, 4, 6 months after transplant surgery) for the APB muscle on the intact side (left side in each map) and biceps muscle on the transplant side (right side in each map). The small arrows close to the coil indicate the posterior-anteriorly directed current induced in the brain. MEP maps for 2 different target muscles performed in 2 experimental sessions were merged in one map. MEP amplitudes for left (0–3 mV) and right hemispheres (0–2 mV) were labeled with different color scales. The centers of gravity of 2 target muscles were labeled with coordinates. The vertex (white cross in each map) was defined as the origin (right and anterior, positive values). The center of gravity for the APB muscle on the intact side was stable over time while that for the biceps muscle on the transplant side progressively shifted in a posterior-medial direction after the transplant surgery. (C) Intracortical inhibitory and facilitatory circuits. The left panels show examples of recordings under various experimental conditions. They were averaged from 10 trials. The right panels show the time course of the intracortical circuits tested. The abscissae indicate the time course. The ordinates indicate the MEP amplitude evoked by paired-pulse stimulation. It is expressed as a percentage of the mean MEP amplitude of test pulse alone (dashed line). Values below 100% indicate inhibition and values above 100% indicate facilitation. The top panel shows IHI at 10 ms (white circle) and 50 ms (black circle) interstimulus intervals. The large arrow indicates the direction of IHI from right to the left hemisphere. Note that both types of IHI from the mirrored position for intact biceps muscle on the transplant side to the intact APB muscle was absent before surgery and gradually increased after the surgery. The bottom panel shows SICI (white circle) and ICF (black circle). SICI in the transplant biceps muscle was absent before surgery and increased gradually after the surgery. ICF did not change. * $p < 0.05$ with Bonferroni's correction for multiple comparisons, comparing MEP amplitude at different time points after surgery to that at baseline (pre-surgery). APB = abductor pollicis brevis; CS = conditioning pulse; ICF = intracortical facilitation; IHI = interhemispheric inhibition; MEP = motor evoked potential; RMT = resting motor threshold; SICI = short-interval intracortical inhibition; TMS = transcranial magnetic stimulation; TS = test pulse.

representations adjacent to the grafted hand tested by neuroimaging and brain stimulation mapping techniques shifted after amputation and returned to their expected positions after hand transplant. The restoration of lost interhemispheric interaction after surgery suggest that pyramidal neurons mediating transcallosal and corticospinal projections undergo plastic changes in a similar manner although the 2 groups of neurons are located in different cortical layers.⁷ The cortical plastic changes may be caused by strengthening or weakening of existing synapses, alterations in neuronal membrane potentials related to changes in ion channels or anatomical changes including sprouting of new axon terminals and formation of new synapses which involve longer term plasticity.³ Our finding that cortical inhibition was decreased in the amputated state was consistent with the opinion that gamma-aminobutyric-acid mediated cortical inhibitory circuit acts as a gate keeper in the induction of cortical plasticity.³ Long-term-potentiation or depression may occur quickly responding to the environment changes and cause the shift of balance between cortical excitation and inhibition. The restoration of lost inhibition after hand transplant is a sign of functional recovery after transplant. The finding that cortical plastic changes occurred at early stages suggest that it may drive recovery and is an important factor in successful recovery of function in the transplanted hand.

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Disclosure

M. Hallett holds patents for an immunotoxin for the treatment of focal movement disorders and the H-coil for magnetic stimulation; in relation to the latter, he has received license fee payments from the NIH (from Brainsway). He is on the Medical Advisory Boards of CALA Health and Brainsway. He has research grants from Allergan for studies of methods to inject botulinum toxins, Medtronic, Inc. for a study of DBS for dystonia, and CALA Health for studies of a device to suppress tremor. R. Chen serves as Editor-in-Chief of the Canadian Journal of Neurologic Sciences, received honorarium from Allergan, Merz and Ipsen, consulted for NeuroQore, received research support from the Canadian Institutes of Health Research, National Institute of Neurologic Disorders and Stroke, Canada Foundation for Innovation, Ontario Research Fund, National Science and

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Continued

Appendix (continued)

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