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A Model for Functional Recovery and Cortical Reintegration after Hemifacial Composite Tissue Allotransplantation

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Abstract

Background—The ability to achieve optimal functional recovery is important in both face and hand transplantation. The purpose of this study was to develop a functional rat hemifacial transplant model optimal for studying both functional outcome and cortical reintegration in composite tissue allotransplantation.

Methods—Five syngeneic transplants with motor and sensory nerve appositions (group 1) and five syngeneic transplants without nerve appositions (group 2) were performed. Five allogeneic transplants were performed with motor and sensory nerve appositions (group 3). Lewis (RT1^l) rats were used for syngeneic transplants and Brown-Norway (RT1ⁿ) donors and Lewis (RT1^l) recipients were used for allogeneic transplants. Allografts received cyclosporine A monotherapy. Functional recovery was assessed by recordings of nerve conduction velocity and cortical neural activity evoked by facial nerve and sensory (tactile) stimuli, respectively.

Results—All animals in groups 1 and 3 showed evidence of motor function return on nerve conduction testing, whereas animals in group 2, which did not have nerve appositions, did not show electrical activity on electromyographic analysis ($p < 0.001$). All animals in groups 1 and 3 showed evidence of reafferentation on recording from the somatosensory cortex after whisker stimulation. Animals in group 2 did not show a cortical response on stimulation of the whiskers ($p < 0.001$).

Conclusion—The authors have established a hemiface transplant model in the rat that has several modalities for the comprehensive study of motor and sensory recovery and cortical reintegration after composite tissue allotransplantation.

Severe defects of the hand and face from trauma, burns, tumor extirpation, congenital abnormalities, and other disfiguring diseases present a reconstructive challenge. Traditional methods of reconstruction, such as skin grafts, local flaps, and free tissue transfer, often fail to achieve adequate aesthetic and functional results. In particular, defects of the hands and multiple subunits of the face, including the nose and lips, are not easily recreated with conventional autologous reconstruction. Allografts from cadaveric sources provide the opportunity for a functional graft and eliminate donor-site morbidity while using a similar tissue type.^{1–3}

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The ability to achieve optimal functional recovery is important in both face and hand transplantation. Hand transplants have shown adequate but variable motor and sensory recovery.¹ Reports from the first face transplant are promising, with some sensation and motor recovery reported as early as 4 months after transplant, and with hopes of continued improvement.⁴

Studies of functional outcome in both hand and face transplantation have led to exploration of the cortical ramifications of composite tissue allografts. Functional magnetic resonance imaging has shown activity in previously quiescent areas of the sensorimotor cortex after composite tissue allografting in both hand and face transplants.^{4–8} For example, functional magnetic resonance imaging studies of a bilateral hand transplant recipient showed that new peripheral inputs from the hand transplant enabled an organized global remodeling of the hand cortical region and reversed cortical reorganization induced by amputation.⁵ Studies of peripheral nerve injury have suggested a correlation between functional recovery and functional remodeling of cortical representational maps.⁹ Thus, examining cortical changes after composite tissue allografting could contribute to understanding functional outcome.

The continued use of composite tissue allografts worldwide accentuates the need for further animal studies to maximize functional outcome. Currently, there is no animal model that provides information on both functional recovery and cortical reintegration in composite tissue allografts. The purpose of our study was to develop a functional rat hemifacial transplant model optimal for studying both functional outcome and cortical reintegration.

The functional unit of the rat face is a specialized structure called the mystacial pad. It contains the vibrissae, or whiskers, which perform a rhythmic sweeping called “whisking” to assess the three-dimensional shape of an object.^{10–13} The buccal and marginal mandibular branches of the facial nerve primarily provide motor innervation to the mystacial pad. They innervate the intrinsic muscles of the mystacial pad, which are responsible for protraction of the whiskers; retraction occurs by passive properties of the skin and by extrinsic mystacial pad musculature.

The infraorbital branch of the maxillary division of the trigeminal nerve provides sensory innervation to the mystacial pad.^{10,14–16} As the rat actively sweeps its vibrissae, each movement activates the mechanoreceptors in the whisker follicle. These receptors transduce mechanical energy into electrical impulses and send signals to brainstem trigeminal nuclei by means of the infraorbital nerve. From the trigeminal nuclei, the signal goes to the contralateral thalamus and somatosensory cortex. The neuron clusters in the somatosensory cortex associated with the vibrissae are called “barrels” because of their characteristic three-dimensional shape. It has been confirmed through extensive study that each barrel in the somatosensory cortex corresponds to a vibrissa in a 1:1 relationship. The barrel cortex of rats, because of its clear columnar structure and direct correlation to individual whiskers on the face, has become a popular model for studying changes of cortical representational maps (Fig. 1).^{17–20}

MATERIALS AND METHODS

Animals

Eight- to 10-week-old inbred rats were used for transplants (Harlan Sprague-Dawley, Indianapolis, Ind.). Lewis (RT1^l) rats were used for syngeneic transplants and Brown-Norway (RT1ⁿ) donors and Lewis (RT1^l) recipients were used for allogeneic transplants. All animals received care in compliance with the University of Pittsburgh Institutional Animal Care and Use Committee and followed guidelines from the *Guide for the Care and Use of Laboratory Animals* published by the National Institutes of Health. The University of

Pittsburgh provided veterinary care in a specific pathogen– free animal facility. The animals were provided rat chow and water ad libitum and caged individually with a 12-hour light/dark cycle.

Surgical Care

All operations were performed under sterile conditions, with animals kept on a heating pad (Braintree Scientific, Inc., Braintree, Mass.) to maintain a constant body temperature of 37°C. Induction of anesthesia was performed with 50 mg/kg of sodium pentobarbital administered intraperitoneally, with maintenance of anesthesia with 10 mg/kg per hour. Glycopyrrolate (0.5 mg/kg) was administered intramuscularly immediately after initial induction of therapy to reduce secretions. A bolus of lactated Ringer's solution (5 ml) was administered to each recipient after transplantation.

Animal Groups

Five syngeneic transplants with motor and sensory nerve appositions (group 1) and five syngeneic transplants without nerve appositions (group 2) were performed. Five allogeneic transplants were performed with motor and sensory nerve appositions (group 3).

Surgical Procedure

Preparation of Functional Hemiface Transplant Donor—An incision was made midline in the neck through the skin and platysma. The external jugular vein was isolated, as were its branches, the posterior and anterior facial veins. The submandibular gland was excised after ligation of its supplying artery and vein. The sternocleidomastoid was then retracted, exposing the common carotid artery. The common carotid artery was exposed distally to the posterior belly of the digastric muscle. The posterior belly of the digastric was excised, exposing the greater horn of the hyoid bone. The internal carotid artery, superior thyroid artery, ascending pharyngeal artery, lingual artery, ascending palatine artery, and internal maxillary artery were transected and ligated. The facial artery was preserved, as was the extension of the external carotid artery. The mystacial pad was elevated partially to expose the infraorbital nerve, which was transected at the level of the periosteum. The entire mystacial pad was then undermined and elevated. The tendinous insertion of the masseter into the periosteum was transected and a small portion of the masseter was elevated from the periosteum. The buccal and marginal mandibular branches of the facial nerve were located anterior to the masseter. The piece of masseter was elevated solely to ease the elevation of the nerves and was not included as a functional part of the graft. The entire flap was elevated from the distal end of the mystacial pad to the ear and midline in the scalp and neck. The periorbital skin was spared. The internal maxillary vein in the retroauricular region was ligated and transected. The common carotid artery and external jugular vein were transected proximally to serve as the vascular pedicle of the flap. The flap was perfused with heparinized lactated Ringer's solution (Figs. 2 and 3).

Preparation of the Recipient—The mystacial pad was elevated to expose the infraorbital nerve, which was transected distally, just as it entered the muscles of the mystacial pad. The entire mystacial pad and subcutaneous tissue of the face extending to the ear on the same side as the donor flap was removed. The masseter muscle and the buccal and marginal mandibular branches of the facial nerve were left intact and isolated. The external jugular vein was isolated and prepared for venous anastomosis. The sternocleidomastoid muscle was retracted to expose the common carotid artery for anastomosis.

Transplantation and Flap Insetting—The functional hemifacial flap was secured onto the recipient with three interrupted 4-0 chromic sutures. The venous anastomosis of the external jugular vein and arterial anastomosis of the common carotid artery of donor and recipient were performed using standard end-to-end microsurgical technique under microscopic magnification with 10-0 nylon sutures. The masseter muscle of the flap was undermined and retracted to expose the buccal and marginal mandibular branches of the facial nerve, which were transected and elevated. Apposition of the buccal and marginal mandibular branches of the facial nerves of the donor and recipient were performed with interrupted stitches on the medial and lateral aspects of the nerve. Apposition of the infraorbital nerve was then performed with a running 10-0 nylon epineurial stitch. Insetting was completed with a running stitch of 6-0 fast-absorbing plain gut suture (Fig. 4).

Postoperative Care—Rats were given Transgel (Charles River Laboratories, Inc., Wilmington, Mass.) and a powder form of rat chow to ease oral consumption in the postoperative period and to maintain proper weight gain. All recipients were given buprenorphine, 0.05 mg/kg subcutaneously every 12 hours for 72 hours, for postoperative analgesia and a 5-ml bolus of lactated Ringer's solution once per day for 3 days. Animals were weighed daily until their preoperative weight was recovered and their general health was monitored as well.

Immunosuppressive Protocol

The animals in the allograft treatment group (group 3) were given cyclosporine A, 16 mg/kg per day, from postoperative day 0 to postoperative day 14. They were then given 13 mg/kg per day until postoperative day 80, after which time they were given 10 mg/kg per day and maintained at that dose.

Clinical Evaluation

Animals were evaluated in the immediate postoperative period for flap loss, ability to resume eating and drinking, weight loss, and general health. On the transplanted side, animals were evaluated for clinical signs of denervation through the presence of fibrillations. Return of motor function was evaluated by noting the return of whisking. In addition, allografts were monitored for clinical signs of rejection, including erythema, edema, desquamation, and necrosis. All animals were evaluated for signs of stroke, such as paresis and weakness in the body contralateral to the transplanted side.

Nerve Conduction Testing

Nerve conduction testing was performed at 12 weeks postoperatively to evaluate the presence or absence of facial nerve-mediated electrical activity. The rat was anesthetized with intraperitoneal sodium pentobarbital (50 mg/kg). The buccal and marginal mandibular branches of the facial nerve were stimulated using a pair of stainless steel wires placed lightly on the exposed nerve; stimuli consisted of brief (0.15 msec) current pulses of 5 mA. Evoked electrical activity was recorded through stainless steel microwires placed in the intrinsic muscles of the mystacial pad. The efficacy of facial nerve stimulation was also assessed by observing the presence or absence of evoked whisker movements.

Cortical Testing

Cortical sensory testing was performed at 20 weeks after transplantation. The rat was anesthetized with intravenous sodium pentobarbital (25 mg/kg). A small craniectomy was made over the whisker representation in the primary somatosensory cortex contralateral to the facial transplant. Insulated, fine-tipped stainless steel microelectrodes with impedances of 2 to 4 M Ω were advanced perpendicularly into the cortex using a hydraulic microdrive.

Whiskers were stimulated with a handheld probe, and stimulus-driven units were isolated and recorded using a waveform amplitude discriminator and a digital oscilloscope. A lesion was made at 800 μm in the cortex with 7mA of current (10 seconds) to mark the location of microelectrode penetration in the cortex. The animal was killed after cortical testing and the brain was perfused with 8% paraformaldehyde solution.

Statistical Analysis

For nerve conduction and cortical testing, if electrical activity was initiated, the animal was given a score of 1; if no electrical activity was elicited, a score of 0 was given. The probability values were obtained with a Fisher's exact test; a two-sided value of $p < 0.05$ was accepted as statistically significant.

Histologic Evaluation

For confirmation that cortical testing was performed in the primary somatosensory cortex, the cortex was sectioned in the tangential plane, reacted for cytochrome oxidase, and counterstained with Nissl. The locations of cortical microelectrode penetrations and lesions were identified with respect to the barrels in the primary somatosensory cortex.

RESULTS

Clinical Evaluation

The mean time for the surgical procedure was 5 hours, with an average warm ischemia time of 90 minutes. No flap necrosis was observed, and all animals survived until the study endpoint of 140 days. In the immediate postoperative period, all rats exhibited a lack of coordination from the loss of tactile sensation on the transplanted side that resolved within 1 day when the rats learned to compensate. All animals were eating and drinking by postoperative day 1. The syngeneic transplants (groups 1 and 2) had an average weight loss of 11.7 percent in the first postoperative week and regained their preoperative weight at an average of 16 days. The average weight loss for the allogeneic transplants (group 3) was 15 percent in the first postoperative week, with resumption of preoperative weight at an average of 20 days. In the allograft group, none of the flaps showed clinical signs of rejection. No animals exhibited evidence of stroke.

Fibrillations began in group 1 on average 8 days after transplantation. In group 3, fibrillations were seen 7 days after transplantation on average. In group 2, fibrillations began 8 days after transplantation and lasted throughout the entire study period of 140 days. Group 1 showed return of whisking an average of 17 days after transplantation. No animals in group 2 showed evidence of whisking throughout the entire study period. Animals in group 3 showed return of whisking an average of 20 days postoperatively (Fig. 5).

Complications

All animals experienced an extensive amount of edema between postoperative days 1 and 7. In addition, mild seromas were observed under some flaps in the first postoperative week. These cases did not require drainage and resolved within the first 2 weeks after transplantation. Three syngeneic transplants exhibited sloughing of the skin just anterior to the transplanted ear, presumably from scratching and grooming. Hair growth resumed approximately 2 weeks after the initiation of the skin sloughing.

Nerve Conduction Testing

All animals in groups 1 and 3 showed evidence of motor function return on nerve conduction testing, whereas animals in group 2, which did not have nerve appositions, did

not show electrical activity. There was a statistically significant difference between the groups with nerve appositions (groups 1 and 3) and group 2 ($p = 0.0007$) (Fig. 6).

Cortical Testing

All animals in groups 1 and 3 showed evidence of reafferentation on recording from the somatosensory cortex after whisker stimulation. There was a statistically significant difference between the groups with nerve appositions (groups 1 and 3) and group 2 ($p = 0.0007$) (Fig. 7).

Histologic Assessment

Electrode tracts and lesions were identified readily by means of barrel cortex histologic evaluation, confirming that testing was performed in the appropriate region of the somatosensory cortex (Fig. 8).

DISCUSSION

Composite tissue allografts present a viable option for reconstruction of complicated defects of the hand and face. The facial skin has a unique texture and elasticity that enables characteristic facial expression that reconstruction with other tissues in the body cannot mimic.²¹ Similarly, the ability of the fingertips to discriminate size, shape, and texture and perform fine movements distinguishes hand transplantation from conventional prostheses.²² Given that the unique characteristics of the hand and face are related to movement and sensation, optimal functional recovery is the ultimate goal in composite tissue allografting.

We have established a hemifacial transplant model in the rat that is ideal for studying functional outcome in composite tissue allografting. The transplant can be performed with little morbidity and mortality. Several facial transplant models were initially introduced in the rat, including a full face and scalp allograft, and hemifacial and hemiface/calvarial grafts.^{23,24} However, these transplant models did not include a functional component. Landin and Cavadas then proposed the “mystacial pad flap,” which included just the mystacial pad and motor and sensory nerves as a possible flap for transplantation.¹⁰ Our model enhances the previously reported models, with inclusion of the mystacial pad and extension to the entire hemiface.

In addition to enhancing current hemifacial transplant models, we performed clinical and electrophysiologic tests to prove that our graft was functional. Our findings of a significant difference on nerve conduction testing between groups with motor nerve appositions (groups 1 and 3) compared with the group (group 2) with no nerve apposition confirmed that our model had motor recovery. Our findings from nerve conduction testing were supported by the fact that initial fibrillations in the mystacial pad of transplants with nerves eventually acquiesced and whisking resumed. Fibrillations are a sign of denervation, but whisking is a sign of reinnervation.²⁵ As expected, fibrillations remained throughout the study period in group 2 because animals in this group did not have nerves transplanted and remained denervated. Our functional transplants also contained an afferent, sensory component, evidenced by the fact that animals in groups 1 and 3 had significant electrical activity in the cortex on stimulation of the whiskers, whereas animals in group 2 did not.

There are several advantages to using our model for the study of functional outcome in composite tissue allografting. The rat vibrissae system comprises both sensitive sensory and motor systems and thus is suited for studying changes in either modality. The rat vibrissal system provides a means with which to mimic the intricate nature of facial reanimation associated with functional face transplants and is well suited for movement analysis tests. Video analysis of vibrissal velocity, amplitude, and whisking pattern and electromyographic

recordings from the mystacial pad are some methods of quantification of facial nerve function and motor recovery. Cortical monitoring after vibrissal manipulation and texture discrimination tests can be used for the clinical assessment of return of sensation.¹⁵

The hemiface transplant model can also be considered superior to the hind limb transplant model when specifically focusing on the study of sensation after composite tissue allografting. The rat vibrissae much more closely emulate the tactile sensation of the fingertips than the hind limb. Like humans and their fingertips, rats encode tactile features of their environment through their vibrissae. The human hand and the whisker follicle share similarities in mechanoreceptors and cell types. Both have slowly adapting mechanoreceptors, such as Merkel cells and Ruffini endings, and rapidly adapting mechanoreceptors.^{26,27}

Cortical testing for reafferentation performed with this model provides objective evidence of sensory recovery, which is often difficult to obtain in rodents. Quantification of sensory recovery can be performed by assessing the amplitude of electrical responses in the cortex.¹⁵ The ability to study cortical reintegration after composite tissue allografting is another advantage of our model. Studies of peripheral nerve injury have shown the ability of the somatosensory cortex to reorganize during recovery.²⁸ Our model allows for the detailed examination of cortical remodeling and changes in mapping after composite tissue allografting given the 1:1 correlation of each vibrissa to a corresponding region in the somatosensory cortex.²⁹

CONCLUSIONS

We have established a functional hemiface transplant model in the rat that has several modalities for the comprehensive study of motor and sensory recovery and cortical reintegration after composite tissue allografting. This model can also be used to examine functional recovery in the setting of tolerance and long-term immunosuppression in composite tissue allografting.

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Fig. 1. Each whisker on the rat face corresponds on a 1:1 basis to a cluster of neurons called a barrel in the primary somatosensory cortex. The barrel cortex of rats, because of its clear columnar structure and direct correlation to individual whiskers on the face, has become a popular model for studying changes of cortical representational maps.

Fig. 2.
A donor flap, including the entire hemiface with the mystacial pad.

Fig. 3.

The underside of the hemifacial flap, showing the common carotid artery (*CCA*), external jugular vein (*EJV*), infraorbital nerve (*ION*), and masseter muscle. The buccal and marginal mandibular facial nerve branches are located underneath the masseter muscle.

Fig. 4. Nerve apposition of the infraorbital nerve of both donor and recipient in a syngeneic transplant.

Fig. 5.
A syngeneic transplant (*left*) and an allogeneic (*right*) transplant at postoperative week 12.

Fig. 6. The nerve conduction testing of a hemifacial transplant with nerve appositions (*above*, experimental) shows electrical activity (*asterisk*), whereas nerve conduction testing of a transplant without nerve appositions (*below*, control) did not elicit electrical activity. The *arrow* indicates stimulation artifact.

Fig. 7. Deflection of the whisker upward (*single arrow*) in a syngeneic transplant at postoperative week 20 with nerve appositions elicited an “on” response (*single asterisk*), whereas return of the whisker to its normal position (*double arrows*) elicited an “off” response (*double asterisks*) of cells in the somatosensory cortex. The “on” and “off” responses indicated cortical reintegration of the flap, with return of ability of the cortex to respond to peripheral stimuli.

Fig. 8. Histologic image of the primary somatosensory cortex with cytochrome oxidase staining, Nissl counterstain, and blue filter. Histologic evaluation confirmed that the lesion (*arrow*) was located in the barrel cortex and thus testing was performed in the proper region of the somatosensory cortex. The *asterisk* indicates a barrel.